

Cochrane Database of Systematic Reviews

Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Abdelhamid AS, Martin N, Bridges C, Brainard JS, Wang X, Brown TJ, Hanson S, Jimoh OF, Ajabnoor SM, Deane KHO, Song F, Hooper L

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[Intervention Review]

Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Asmaa S Abdelhamid¹, Nicole Martin², Charlene Bridges², Julii S Brainard¹, Xia Wang¹, Tracey J Brown¹, Sarah Hanson³, Oluseyi F Jimoh¹, Sarah M Ajabnoor¹, Katherine HO Deane³, Fujian Song¹, Lee Hooper¹

¹Norwich Medical School, University of East Anglia, Norwich, UK. ²Farr Institute of Health Informatics Research, University College London, London, UK. ³School of Health Sciences, University of East Anglia, Norwich, UK

Contact address: Lee Hooper, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, Norfolk, NR4 7TJ, UK. l.hooper@uea.ac.uk.

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ABSTRACT

Background

Evidence on the health effects of total polyunsaturated fatty acids (PUFA) is equivocal. Fish oils are rich in omega-3 PUFA and plant oils in omega-6 PUFA. Evidence suggests that increasing PUFA-rich foods, supplements or supplemented foods can reduce serum cholesterol, but may increase body weight, so overall cardiovascular effects are unclear.

Objectives

To assess effects of increasing total PUFA intake on cardiovascular disease and all-cause mortality, lipids and adiposity in adults.

Search methods

We searched CENTRAL, MEDLINE and Embase to April 2017 and clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform to September 2016, without language restrictions. We checked trials included in relevant systematic regions.

Selection criteria

We included randomised controlled trials (RCTs) comparing higher with lower PUFA intakes in adults with or without cardiovascular disease that assessed effects over 12 months or longer. We included full texts, abstracts, trials registry entries and unpublished data. Outcomes were all-cause mortality, cardiovascular disease mortality and events, risk factors (blood lipids, adiposity, blood pressure), and adverse events. We excluded trials where we could not separate effects of PUFA intake from other dietary, lifestyle or medication interventions.

Data collection and analysis

Two review authors independently screened titles and abstracts, assessed trials for inclusion, extracted data, and assessed risk of bias. We wrote to authors of included trials for further data. Meta-analyses used random-effects analysis, sensitivity analyses included fixed-effects and limiting to low summary risk of bias. We assessed GRADE quality of evidence.

Main results

We included 49 RCTs randomising 24,272 participants, with duration of one to eight years. Eleven included trials were at low summary risk of bias, 33 recruited participants without cardiovascular disease. Baseline PUFA intake was unclear in most trials, but 3.9% to 8% of total energy intake where reported. Most trials gave supplemental capsules, but eight gave dietary advice, eight gave supplemental foods such as nuts or margarine, and three used a combination of methods to increase PUFA.

Increasing PUFA intake probably has little or no effect on all-cause mortality (risk 7.8% vs 7.6%, risk ratio (RR) 0.98, 95% confidence interval (CI) 0.89 to 1.07, 19,290 participants in 24 trials), but probably slightly reduces risk of coronary heart disease events from 14.2% to 12.3% (RR 0.87, 95% CI 0.72 to 1.06, 15 trials, 10,076 participants) and cardiovascular disease events from 14.6% to 13.0% (RR 0.89, 95% CI 0.79 to 1.01, 17,799 participants in 21 trials), all moderate-quality evidence. Increasing PUFA may slightly reduce risk of coronary heart disease death (6.6% to 6.1%, RR 0.91, 95% CI 0.78 to 1.06, 9 trials, 8810 participants) and stroke (1.2% to 1.1%, RR 0.91, 95% CI 0.58 to 1.44, 11 trials, 14,742 participants, though confidence intervals include important harms), but has little or no effect on cardiovascular mortality (RR 1.02, 95% CI 0.82 to 1.26, 16 trials, 15,107 participants) all low-quality evidence. Effects of increasing PUFA on major adverse cardiac and cerebrovascular events and atrial fibrillation are unclear as evidence is of very low quality.

Increasing PUFA intake slightly **reduces total cholesterol** (mean difference (MD) -0.12 mmol/L, 95% CI -0.23 to -0.02, 26 trials, 8072 participants) and **probably slightly decreases triglycerides** (MD -0.12 mmol/L, 95% CI -0.20 to -0.04, 20 trials, 3905 participants), but has little or no effect on high-density lipoprotein (**HDL**) (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, 18 trials, 4674 participants) or low-density lipoprotein (**LDL**) (MD -0.01 mmol/L, 95% CI -0.09 to 0.06, 15 trials, 3362 participants). Increasing PUFA probably causes slight **weight gain** (MD 0.76 kg, 95% CI 0.34 to 1.19, 12 trials, 7100 participants).

Effects of increasing PUFA on **serious adverse events** such as pulmonary embolism and bleeding are unclear as the evidence is of very low quality.

Authors' conclusions

This is the most extensive systematic review of RCTs conducted to date to assess effects of increasing PUFA on cardiovascular disease, mortality, lipids or adiposity. Increasing PUFA intake probably slightly reduces risk of coronary heart disease and cardiovascular disease events, may slightly reduce risk of coronary heart disease mortality and stroke (though not ruling out harms), but has little or no effect on all-cause or cardiovascular disease mortality. The mechanism may be via lipid reduction, but increasing PUFA probably slightly increases weight.

PLAIN LANGUAGE SUMMARY

Polyunsaturated fatty acids for prevention and treatment of diseases of the heart and circulation

Review question

We reviewed randomised trials (participants have an equal chance to be assigned to either treatment) examining effects of increasing intake of polyunsaturated fatty acids (PUFA) on deaths and diseases of the heart and circulation (cardiovascular diseases), including heart attacks and stroke.

Background

We eat PUFA in our usual food, but quantities of PUFA eaten vary. There is some evidence that increasing the amount of PUFA we eat can reduce our blood cholesterol and make us less likely to develop cardiovascular disease, particularly if PUFAs are eaten instead of saturated fats (fats from animal sources such as meat and cheese). But eating more PUFA may increase our body weight, and omega-6 fats (one component of PUFA) may worsen cardiovascular risk by increasing inflammation. Evidence on the benefits or harms of increasing PUFA intake on diseases of the heart and circulation, or on other health outcomes, is inconclusive.

Trial characteristics

Evidence in this Cochrane Review is current to 27 April 2017. We included 49 trials randomising 24,272 participants, for one to eight years. These trials assessed effects of eating more, compared to less PUFA, on diseases of the heart and circulation, and deaths. Twelve trials were very trustworthy (had low risk of bias overall). Participants were men and women, some with existing illnesses and some not. Trials took place in North America, Asia, Europe and Australia, and sixteen were funded only by national or charitable agencies.

Key results

Increasing PUFA probably makes little or no difference (neither benefit nor harm) to our risk of death (moderate-quality evidence), and may make little or no difference to our risk of dying from cardiovascular disease (low-quality evidence). However, increasing PUFA probably slightly reduces our risk of heart disease events and of combined heart and stroke events (moderate-quality evidence). Fifty three people would need to eat more PUFA to prevent one person experiencing a heart disease event, and 63 people to prevent one person experiencing a heart or stroke event. Increasing PUFA may very slightly reduce risk of death due to heart disease, as well as stroke, but harm is possible (low-quality evidence). PUFA probably slightly reduces fats circulating in the blood (cholesterol, high-quality evidence and triglycerides, moderate-quality evidence). Increasing PUFA probably slightly increases body weight (moderate-quality evidence). The evidence mainly comes from trials of men living in high-income countries.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Higher PUFA compared to lower PUFA for CVD

Patient or population: people with or without existing CVD, men and women

Setting: includes free-living participants and those living in institutions. Includes participants from all continents but most events occurred in trials carried out in Europe or

North America.

Intervention: higher PUFA intake Comparison: lower PUFA intake

Eligible trials compared higher with lower total PUFA intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements had to aim to increase or decrease total PUFA intake, or a dietary component high in total PUFA intake such as vegetable oil, or, if no clear aim was stated (but implied, such as aiming to provide a 'heart health', 'reduced fat' or 'Mediterranean' diet) then the intervention had to achieve an increase or decrease of at least 10% of the baseline total PUFA level

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence	Comments
	Risk with lower PUFA Risk with higher PUFA			(GRADE)	
All-cause mortality Follow-up: range 12	No CVD at baseline (primary prevention)	RR 0.98 (0.89 to 1.07)	19,290 (24 RCTs)	$\oplus \oplus \oplus \bigcirc$ Moderate a	Increasing PUFA intake probably has little or no
months to 96 months	34 per 1000 33 per 1000 (27 to 41)				effect on all-cause mortality (risk alters from 7. 8% to 7.6% in the overall
	CVD at baseline (secondary prevention)				study population), mod- erate-quality evidence
	117 per 1000 115 per 1000 (101 to 131)				
Coronary heart disease events Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)	RR 0.87 (0.72 to 1.06)	10,076 (15 RCTs)	⊕⊕⊕⊖ Moderate ^b	Increasing PUFA intake may reduce risk of CHD events (from 14.2% to 12.3% in the study pop- ulation, NNT = 53), mod- erate-quality evidence

	134 per 1000	71 per 1000 (34 to 149)				
	CVD at baseline (se	econdary prevention)				
	143 per 1000	137 per 1000 (122 to 156)				
Stroke Follow-up: range 12 months to 96 months	No CVD at baseline	e (primary prevention)	RR 0.91 (0.58 to 1.44)	14,742 (11 RCTs)	⊕⊕⊖⊖ Low ^c	Increasing PUFA intake may reduce risk of stroke (from 1.2% to 1. 1% in the study population, NNT= 1000), low-
	21 per 1000	15 per 1000 (10 to 24)				
	CVD at baseline (secondary prevention)					quality evidence. How- ever, the 95% confi- dence intervals include
	5 per 1000	6 per 1000 (3 to 13)				important harms as well as benefit
Major adverse car- diac and cerebrovascu- lar events Follow-up: range 24 months to 96 months	No CVD at baseline	e (primary prevention)	RR 0.84 (0.59 to 1.20)	2879 (2 RCTs)	⊕○○○ Very low ^d	Effects of increasing PUFA on MACCEs are unclear as the evidence is of very low quality
	206 per 1000	142 per 1000 (105 to 192)				
	CVD at baseline (secondary prevention)					
	332 per 1000	329 per 1000 (289 to 372)				

^{*}The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; CVD: cardiovascular disease; OR: odds ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^aAll-cause mortality

- 1. **Risk of bias**: effect size did not alter when restricted to trials at low summary risk of bias, low risk of bias from allocation, attention or compliance. Not downgraded.
- 2. **Inconsistency**: consistent effects, I² statistic less than 50%. Not downgraded.
- 3. **Indirectness**: most data came from trials of men, but some were from trials of women or men and women combined. Most events occurred in older participants, but events also occurred in younger and middle-aged participants. Included trials were from all continents but most events occurred in trials carried out in Europe or North America. Not downgraded.
- 4. Imprecision: over 1400 events occurred in trials including over 19,000 participants over at least 12 months. However, 95% CI included important benefits. Downgraded once.
- 5. **Publication bias**: funnel plot did not suggest small study bias, we are aware of few events that could not be added to the meta-analysis. Not downgraded.

^bCoronary heart disease events

- 1. **Risk of bias**: sensitivity analyses restricting trials to low risk of bias for attention and compliance give similar results to the main analysis, as do restricting to trials without industry funding or pre-2010 and trials on trials registries, and larger trials all confirmed a small beneficial effect on coronary heart disease (CHD) events. However, limiting to trials at low risk of bias from allocation concealment and to trials of low summary risk of bias suggest increased CHD risk with more PUFA, making us less certain of the effect of increasing PUFA on this outcome. It was further noted by the WHO NUGAG Subgroup on Diet and Health that although limiting to trials at low risk of bias from allocation concealment and to trials of low summary risk of bias suggest increased CHD risk with more PUFA, results of the most heavily weighted trial are consistent with results of the main analysis, while the next largest trial differs from the main result; therefore, confidence in the results of these analyses is low and the outcome was not downgraded. Not downgraded, but part of the downgrading for imprecision was for risk of bias.
- 2. **Inconsistency**: consistent effects, I² statistic less than 50%. Not downgraded.
- 3. Indirectness: most events occurred in men, and in high-income countries. Not downgraded.
- 4. Imprecision: the 95% confidence intervals did not exclude harm from increased PUFA. Downgraded once (with risk of bias).
- 5. **Publication bias**: funnel plot did not suggest small study bias, we are aware of few events that could not be added to the meta-analysis. Not downgraded.

^cStroke

1. **Risk of bias**: some sensitivity analyses suggested benefit of increased PUFA, some suggested harm or little effect. It was further noted by the WHO NUGAG Subgroup on Diet and Health that in most analyses, the most heavily weighted trials

were consistent with the main results, and the outcome was therefore not downgraded. Not downgraded, but part of the downgrading for imprecision was for risk of bias.

- 2. **Inconsistency**: consistent effects, I² statistic less than 50%. Not downgraded.
- 3. Indirectness: most events occurred in men, and in high-income countries. Not downgraded.
- 4. **Imprecision**: with only 166 participants experiencing a stroke imprecision was high, the 95% confidence intervals did not exclude important harm from increased PUFA. Downgraded twice (with risk of bias).
- 5. **Publication bias**: funnel plot did not suggest small study bias, we are aware of few events that could not be added to the meta-analysis. Not downgraded.

^d Major adverse cardiac and cerebrovascular events (MACCEs)

- 1. **Risk of bias**: neither of the included trials were at low risk from allocation concealment, or at low summary risk of bias. Downgraded once.
- 2. **Inconsistency**: I² statistic = 79%. Downgraded once.
- 3. **Indirectness**: all participants of the included trials were men, and trials were conducted in Europe and North America. Not downgraded.
- 4. Imprecision: 817 people experienced MACCEs, although harm was not excluded by the 95% Cl. Downgraded once.
- 5. Publication bias: not possible to assess with only 2 trials. Not downgraded.

BACKGROUND

Description of the condition

The World Health Organization (WHO) reports cardiovascular diseases as the primary cause of death in the world (WHO 2016). In 2012 they estimated that 17.5 million people died from cardiovascular diseases, three-quarters of whom were in low- to middle-income countries. Cardiovascular diseases are disorders of the heart and blood vessels and include a range of conditions. Some are diseases of blood vessels supplying the heart (coronary heart disease), brain (cerebrovascular disease), or arms or legs (peripheral arterial disease). Others are due to infection (rheumatic heart disease, where damage to the heart muscle and valves is due to rheumatic fever), are present at birth (congenital heart disease), or are due to blood clots (deep vein thrombosis and pulmonary embolism) (WHO 2016). This review is concerned with the forms of cardiovascular disease that are potentially modifiable by dietary means, particularly coronary heart disease and cerebrovascular disease.

Description of the intervention

Polyunsaturated fatty acids (PUFAs) are fats that include at least two double carbon-to-carbon bonds (unsaturated carbon bonds) in their long hydrocarbon chain. This makes the fats pack less well, so they tend to be liquid at room temperature, rather than solid like many saturated fats. PUFAs can be omega-3 (where the first double bond is three carbons away from the methyl-carbon end of the molecule), omega-6 or omega-9 (although most omega-9 fats do not have at least two double bonds, so are not included). Fish and plant oils are often rich in PUFAs, with fish being rich in omega-3 and plant oils rich in omega-6. Two PUFAs, alphalinolenic acid (omega-3) and linoleic acid (omega-6), are essential nutrients in humans.

Dietary fats have been implicated in cardiovascular health since Keys published his groundbreaking study linking plasma cholesterol and dietary saturated fat (Keys 1950), and Oliver reported higher levels of low density lipoprotein (LDL) in those surviving myocardial infarction compared to controls without myocardial infarction (Oliver 1953). In 1965 Hegsted published an equation that quantified the relationship between dietary fat and serum total cholesterol, suggesting that increasing saturated fats increased serum cholesterol, while increasing PUFA reduced serum cholesterol (Hegsted 1965). More recently there has been debate about what type of PUFA may be protective, with interest in omega-3 PUFAs following randomised controlled trials (RCTs) with dietary fish and fish oil supplementation interventions in the 1980s and 1990s (Burr 1989; GISSI-P 1999), although subsequent trials have been equivocal (Abdelhamid 2018; Hooper 2006). Similarly, while there are good theoretical grounds for suggesting that omega-6 fats may be protective against cardiovascular diseases, the RCT evidence is limited (Hooper 2018). However, there is evidence that replacing saturated fats with PUFAs does protect against cardiovascular disease, and that PUFAs appear to be more protective than reducing saturated fats and replacing them with carbohydrates (Hooper 2015a). On the other hand, reducing dietary fat (including PUFAs) appears to result in lower weight in adults, suggesting that lower PUFA intake would tend to protect against cardiovascular disease (Hooper 2015b).

How the intervention might work

PUFAs are generally thought to work by producing a reduction in serum total cholesterol and LDL, which slows the progress of atherosclerosis (a complex syndrome in which plaque builds up inside the arteries over time, reducing blood flow and leading to an increased risk of blood clots), and so delays or prevents the onset of cardiovascular and cerebrovascular disease. This theory is reinforced by evidence that replacing saturated fats with polyunsaturated fats is associated with greater reductions in cardiovascular events and with greater reduction of serum total cholesterol (Hooper 2015a). Additional modes of action have been proposed for omega-3 PUFAs (particularly EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) both fish-based omega-3 polyunsaturated fatty acids. These modes of action include: lowering of blood pressure; reducing thrombotic tendency; anti-inflammatory and antiarrhythmic effects; improving vascular endothelial function; increasing plaque stability (through increased plaque calcification); and improving insulin sensitivity (Calder 2012; Ohwada 2016). Omega-6 PUFAs may reflect the general lipid-lowering effects of PUFAs, but there has been concern that high levels of omega-6 intake can increase production of 2-series prostaglandins and 4-series leukotrienes compared with the 3-series prostaglandins and 5-series leukotrienes associated with omega-3 intake. As the 2-series prostaglandins and 4-series leukotrienes exert a more potent pro-inflammatory effect, omega-6 could increase the risk of cardiovascular disease by promoting inflammation (Russo 2009).

Why it is important to do this review

The evidence on the health effects of total PUFA intake, which is the combination of omega-3 and omega-6 fats, is equivocal. As cardiovascular diseases are important determinants of health, that particularly burden the poorest people (WHO 2016), we need to understand the role of PUFAs to provide the best advice for individuals and populations about how to eat to reduce the risk of ill health. This assessment of health effects of total PUFA intake is needed alongside updated assessment of the effects of omega-3 and omega-6 fats (Hooper 2018; Abdelhamid 2018).

The World Health Organization (WHO) is currently updating its guidance on polyunsaturated fatty acid intake in adults and children. This new review was commissioned by WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health in order to inform and contribute to the development of updated WHO recommendations. The results of this review including GRADE assessments were discussed and reviewed by the WHO NUGAG Subgroup on Diet and Health as part of their guideline development process. This is a new review and forms a set with Abdelhamid 2018 (assessing effects of omega-3 fats), Hooper 2018 (assessing effects of omega-6 fats), reviews of diabetes and glucose tolerance (Brown 2017), inflammatory bowel disease (IBD) (Thorpe 2017), cognition (Jimoh 2017), depression (Hanson 2017a), bone and muscle health (Abdelhamid 2017), and cancers (Hanson 2017b).

OBJECTIVES

To assess effects of increasing total PUFA intake on cardiovascular disease and all-cause mortality, lipids and adiposity in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that compared higher with lower polyunsaturated fatty acid intakes and assessed effects over at least 12 months (12 months' continuous involvement). We included trials reported as full text, those published as abstracts only, as trials registry entries and unpublished data. We did not include cross-over trials (unless we could use data from the first part of the cross-over only), as this design is inappropriate for outcomes such as cardiovascular disease events or mortality, but included cluster-randomised trials, as long as there were at least six clusters (to facilitate equivalence of the arms at baseline).

Types of participants

We included trials of adults (18 years of age and above). Included participants could be adults who were well, or with increased risk of cancer, those undergoing - or who had undergone - coronary artery bypass grafting or angioplasty, and those with current or previous cardiovascular disease, diabetes mellitus, rheumatoid arthritis, depression, cognitive impairment, or multiple sclerosis. We were interested in both primary and secondary prevention, so included people with or without a history of cardiovascular disease.

We excluded participants who were pregnant or acutely ill, and defined acute illness as including people with diagnosed current cancer, undergoing heart or renal transplantation, with HIV or AIDS, on haemodialysis, with immunoglobulin A (IgA) glomerulonephritis, or any other renal problem except diabetic nephropathy. Our reasoning was to exclude people with conditions that may affect the relationship between polyunsaturated fatty acids and cardiovascular disease events.

Where trials included some adults and some people under 18 years of age, then we included the trial if at least 90% of participants were aged 18 years or over at baseline, or where outcomes for adults could be separated from those for younger people.

Types of interventions

Eligible trials compared higher with lower total polyunsaturated fatty acid (PUFA) intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements had to aim to increase or decrease total PUFA intake, or a dietary component high in total PUFA intake such as vegetable oil, or, if no clear aim was stated (but implied, such as aiming to provide a 'heart health', 'reduced fat' or 'Mediterranean' diet), then the intervention had to achieve an increase or decrease of at least 10% of the baseline total PUFA level.

Supplementation had to be in oil or capsule form, or as foodstuffs provided, to be consumed by mouth (we excluded enteral and parenteral feeds, and enemas). Trials were included if they compared the effect of this intervention with usual diet, no advice, no supplementation or placebo (as appropriate) or with a lower PUFA intake.

We did not include trials if they included multiple risk factor intervention on lifestyle factors such as weight reduction, smoking or physical activity goals, or differential dietary interventions not involving dietary fats (such as advice to eat more fruit and vegetables, increase fibre, or take a vitamin supplement), except where that other intervention was a direct replacement for polyunsaturated fatty acids or the effect of the fat intervention could be separated out from the other interventions. Where a single intervention that increased PUFA intake (such as increasing walnuts, sunflower oil or a margarine) included additional nutrients (they all do) we included it, regardless of what nutrients were displaced. We interpreted this consistently across the review.

We made decisions on inclusion using the following decision tree:

- 1. Include if the trial aimed to increase total PUFA regardless of dose (or aimed to increase a combination of omega-3 and omega-6). If not then assess point 2.
- 2. Include if the trial provided within-trial intervention and control group total PUFA intake data, and the difference was 10% or more of the control group total PUFA intake OR the difference was 10% or more of baseline total PUFA intake or an assumed baseline intake of 6% of energy (6% E) from total PUFA. The assumed baseline intake of 6% E from total PUFA was an average from the trials for which there were data, so we

included trials that provided 0.6% E or above (or ≥ 1.33 g/d) more or less total PUFA to the intervention arm compared to control. If not then assess point 3.

3. Include if the trial provided within-trial intervention and control group total PUFA intake aims, and the difference was 10% or more of the control group total PUFA intake OR the difference was 10% or more of baseline total PUFA intake or an assumed baseline intake of 6% E from total PUFA. Where intake information came from trial aims we looked for corroboration that there was a higher total PUFA intake in one arm than the other, using information on control group supplements or advice, body fat markers of total PUFA or serum total cholesterol. Where a suggested higher intake of PUFA in one arm by trial aims was contradicted by biomarker or total cholesterol data (assuming lower total cholesterol with higher PUFA) we excluded. We included trials that provided an additional total PUFA of 0.6% E or more, or 1.33 g/d or more to the intervention arm compared to control (taking into account PUFA content of placebo and excluding if placebo content was unclear). If no inclusion from point 3 then we excluded the trial. We documented our reasoning over inclusion decisions in Characteristics of included studies (see 'Inclusion basis') and reasons for exclusion in Characteristics of excluded studies. We also ran sensitivity analyses on risk of bias from compliance (see Sensitivity analysis).

Types of outcome measures

Primary outcomes

Primary outcomes were:

- 1. all-cause mortality;
- 2. coronary heart disease events: number of participants experiencing at least one myocardial infarction (fatal or non-fatal) or angina;
- 3. stroke (number of participants experiencing an ischaemic and/or haemorrhagic stroke); and
- 4. major adverse cardiac and cerebrovascular events (MACCEs, used where we could assess the numbers of participants experiencing fatal or non-fatal myocardial infarction, unstable angina or stroke).

Secondary outcomes

Secondary outcomes were all systematically reviewed. If any trial fulfilled the other inclusion criteria and reported a secondary outcome (even if no primary outcomes were reported) we included it. Secondary outcomes included:

- 1. cardiovascular mortality (deaths due to cardiovascular causes including myocardial infarction and stroke)
- 2. cardiovascular events (all available data on number of participants experiencing any of fatal and non-fatal myocardial infarction, angina and/or stroke);

- 3. coronary heart disease mortality;
- 4. myocardial infarction;
- 5. sudden cardiac death;
- 6. atrial fibrillation (arrhythmias including atrial fibrillation, ventricular fibrillation and ventricular tachycardia);
 - 7. angina;
- 8. heart failure:
- 9. Peripheral arterial disease (PAD);
- 10. revascularisation (participants experiencing angioplasty or coronary artery bypass grafting);
- 11. measures of adiposity (including body weight, body mass index (BMI), waist circumference, percentage body fat);
- 12. serum lipids (including total cholesterol, fasting triglycerides, high-density lipoprotein (HDL) and low density lipoprotein (LDL)).

Tertiary outcomes

Tertiary outcomes (not formally systematically reviewed) included:

- 1. blood pressure (systolic and diastolic);
- 2. quality-of-life measures (such as feelings of health and time off work);
 - 3. economic costs;
- 4. serious adverse events (all serious adverse events presented were collated but cancers, inflammatory bowel disease, neurocognitive outcomes such as dementia, diabetes, functional outcomes and depression are not reported here);
 - 5. dropouts.

We included trials where data on any primary or secondary outcome were available in published reports or based on contact with trial authors. We collated data on tertiary outcomes where they were present in included trials. Data on cancers (Hanson 2017b), inflammatory bowel disease (Thorpe 2017), neurocognitive outcomes including dementia (Jimoh 2017), diabetes (Brown 2017), bone and muscle outcomes (Abdelhamid 2017) and depression (Hanson 2017a) are reported fully and systematically in associated reviews within this series, rather than a subset being presented within this review.

Where it was clear that no participants experienced a particular primary or secondary outcome (and the study had not collected data on other primary or secondary outcomes) we excluded the trial. For example, on exploration, a number of trial authors confirmed that no participants had died or experienced heart attacks in their trials; in the absence of other primary or secondary outcomes being recorded we excluded these from this review and noted them in the exclusion list. Their inclusion into the review would have swollen the size of the review without adding any useful data.

Key outcomes

When the WHO NUGAG Subgroup on Diet and Health requested this review they named the following as key outcomes to inform their planned dietary guidance:

- 1. all-cause mortality;
- 2. cardiovascular disease mortality;
- 3. cardiovascular disease events
- 4. coronary heart disease mortality
- 5. coronary heart disease events
- 6. stroke
- 7. atrial fibrillation (arrhythmia)
- 8. serum lipids including total cholesterol, fasting triglycerides, HDL and LDL; and
 - 9. measures of adiposity (body weight and BMI)

We were not able make all of these primary outcomes. However, because WHO NUGAG Subgroup on Diet and Health will use these outcomes to underpin guidance, we carried out sensitivity analyses, subgroup analyses and GRADE assessment of quality of evidence for them, even when they were not primary outcomes. All of these outcomes were formally systematically reviewed.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases on 27 April 2017 to identify reports of relevant randomised controlled trials:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 4) in the Cochrane Library;
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 27 April 2017);
 - Embase Classic and Embase (Ovid, 1947 to 27 April 2017).

We adapted the search strategy for MEDLINE (Ovid) from the search strategy in Hooper 2018 and also used it to locate trials to update Hooper 2018. This complex strategy was adapted for use in the other databases (Appendix 1). We applied the Cochrane sensitivity and precision-maximising RCT filter to MEDLINE (Ovid), and for Embase, we applied terms recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2011). As we were also running searches for, updating and extending, another existing Cochrane Review of the effects of omega-3 fats on health outcomes (Abdelhamid 2018), and there was a great deal of overlap between the searches, the omega-3 searches were also run to May 2017, using the same RCT filters (Appendix 2). The results of these searches were de-duplicated with the results from the searches for this review and all the titles and abstracts assessed as a single set. We created a dataset of RCTs that compared higher versus lower omega-6 fats, omega-3 fats or total PUFA in adults with a duration of at least 6 months. We used this dataset as the wider trial pool from which to select included trials for all the systematic reviews in this series (Abdelhamid 2016; Abdelhamid

2017; Abdelhamid 2018; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Hooper 2018; Thorpe 2017).

We searched two clinical trials registers, ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP, www.who.int/ictrp/en/) during September 2016 for registry entries for relevant completed and ongoing trials.

Searching other resources

We checked included trials of relevant systematic reviews, and wrote to authors of included studies for additional trials and trial data (including unpublished outcome data).

We attempted to obtain full-text translations or evaluations of all relevant non-English articles. Where these were not available we translated papers ourselves using our existing language skills and language translation software.

Data collection and analysis

Selection of studies

Two review authors independently screened titles and abstracts identified by the searches and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. All review authors carried out screening. All articles coded for retrieval by either reviewer were collected in full text. We retrieved full-text study reports/publications and two review authors independently screened the full text, assessed studies for inclusion, and identified and recorded reasons for exclusion of ineligible trials (LH and AA). We resolved any disagreement through discussion. Where a trial met our inclusion criteria with the exception that they did not report any relevant outcome, we wrote to the trial author to ask whether any relevant outcomes occurred. We excluded trials when no relevant primary or secondary outcome events had occurred and the trial had not collected any data on our primary or secondary continuous outcomes.

We identified and collated multiple reports of the same trial (as each trial, rather than each report, was the unit of interest in the review). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009).

Data extraction and management

We developed a draft data collection form for collating study characteristics and outcome data, then all review authors piloted the form on a single included trial to standardise data extraction and improve the data extraction form. All review authors took part in data extraction. Two review authors each extracted the following characteristics from included trials, independently in duplicate:

1. bibliographic details;

- 2. trial registration database and number;
- 3. methods: trial design, total trial duration, details of any 'run in' period, number of study centres and location, trial setting, withdrawals, and trial dates;
- 4. participants: number randomised in each arm, number analysed in each arm, mean age, age range, gender, health status, cardiovascular disease risk and a brief description of participants. We categorised baseline cardiovascular risk as primary prevention (participants not included on the basis of having existing cardiovascular disease) and secondary prevention (participants included on the basis of existing cardiovascular disease, such as angina or a previous stroke or myocardial infarction);
- 5. interventions: intervention (including composition and dose of PUFA intake advised or supplement used), comparison, concomitant medications, and excluded medications;
- 6. outcomes: primary, secondary and tertiary outcomes specified in trial registry, data on outcomes reported in publications and by contact with authors, time points reported. We assessed dichotomous outcomes at the latest point of available follow-up within the trial, while we assessed continuous outcomes at the latest point available in the trial (and after at least 12 months);
- 7. process data: intake data (mean and standard deviation (SD) of total PUFA, omega-3, omega-6, total fat, saturated fat, monounsaturated fat (MUFA), carbohydrate, protein, energy, alcohol and trans fat intake), biomarker data (erythrocyte, serum or adipose tissue fatty acid status data) and serum total cholesterol in intervention and control groups at latest point available during RCT;
- 8. study funding and notable conflicts of interest of trial authors

We resolved disagreements between data extractions by consensus or by involving a third person (LH or AA). One review author (AA or LH) transferred data into the Review Manager 5 (RevMan 5) file (RevMan 2014). We double-checked that data had been entered correctly from the agreed data extraction by comparing the data presented in the systematic review with data extraction (AA, JB, TJB or LH).

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each trial, alongside data extraction, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). All review authors carried out data extraction and assessment of risk of bias. We resolved disagreements by discussion or by involving another author (LH or AA). We assessed the risk of bias according to the following domains:

- 1. random sequence generation (selection bias);
- 2. allocation concealment (selection bias);
- 3. blinding of participants and personnel (performance bias);
- 4. blinding of outcome assessment (detection bias);
- 5. incomplete outcome data (attrition bias);

- 6. selective outcome reporting (reporting bias);
- 7. attention bias (another aspect of performance bias, where the intervention or control groups receive more time and/or attention from trial or health personnel during the trial); and
- 8. compliance (to be assessed as at low risk of bias regarding compliance, the higher PUFA arm had to demonstrate an increase in PUFA over control in a body biomarker (total PUFA had to be assessed by at least linoleic acid plus one or more further components of PUFA), or greater reduction in total cholesterol in the higher PUFA arm. Where lipid biomarker and total cholesterol contradicted each other we chose unclear.
 - 9. other risk of bias

These are the domains of the Cochrane 'Risk of bias' tool, with the exceptions of attention bias and compliance, which were specific to our review and added after discussion with the WHO NUGAG Subgroup on Diet and Health. We followed recommendations in Higgins 2011a, recording funding data in the Characteristics of included studies but not using them as a separate issue for assessing risk of bias.

We graded each potential source of bias as high, low or unclear risk and provided trial details, a quote from the trial report, or both, together with a justification for our judgment in the 'Risk of bias' tables. We assessed summary risk of bias for each trial. Where information on risk of bias related to unpublished data or correspondence with a trial author, we noted it in the 'Risk of bias' tables. Further details of how we interpreted the risk of bias elements across trials are found in Table 1.

Summary risk of bias

Schultz 1995 found that poorly concealed allocation was associated with a 40% greater effect size and so randomisation and allocation concealment are core issues for all trials. Lack of blinding is associated with bias, though smaller levels of bias than lack of allocation concealment (Savovic 2012), especially in trials with objectively measured outcomes (Wood 2008). Most of our outcomes were objectively measured. Although we originally planned to assess summary risk of bias in the same way across all trials in this Cochrane Review, the omega-3 Cochrane Review and the omega-6 Cochrane Review (Abdelhamid 2016; Abdelhamid 2018; Hooper 2018) we adopted a different approach after discussing the different nature of supplement trials compared to dietary advice or food provision trials with the NUGAG Subgroup on Diet and Health. We considered a supplement or capsule-type trial to be at low summary risk of bias, where we judged randomisation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors adequate. We considered all other trials at moderate or high risk of bias (a single category).

We considered a dietary-advice or all-food-provided-type trial to be at low summary risk of bias, where we judged randomisation, allocation concealment, and blinding of outcome assessors adequate. We considered all other trials at moderate or high risk of bias (a single category).

Assessment of bias in conducting the systematic review

We conducted this Cochrane Review according to the published Cochrane protocol and reported any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous data as mean difference (MD) with 95% CIs. We presented continuous data with a consistent direction of effect (as a smaller reading is generally positive), with the exception of HDL, where an increase is positive.

We used change data (change from baseline to latest point in trial in each arm) for continuous data where available with appropriate variance data. When change data were not available we used absolute data from the latest point in each trial arm, unless baseline data were too different between arms. (We considered baseline data too different to use when the change in both arms, from baseline to end data, was smaller than the baseline difference between arms). Where continuous data were too different to use this we noted it in the outcome section of Characteristics of included studies but we did not add data to meta-analyses.

We intended narrative description of skewed data reported as medians (without variance data or with interquartile ranges). We added these data to forest plots so that there could be visual comparison of findings (though we did not include these data in meta-analyses). We intended to use standardised mean differences (SMD) to combine data where included trials had used different scales to measure the same factor (such as quality of life). We did not find any such data, so did not use SMD. We converted data on different scales to the same scale, such as mg/dL and mmol/L for lipids.

Unit of analysis issues

Trials with multiple intervention groups

Where trials included more than two arms we assessed all arms for inclusion. Where there were more than one intervention arm and a single control arm we combined dichotomous and continuous data for the intervention arms and compared them to the single control arm. This meant there were no problems with trial participants appearing more than once in any forest plot.

Cluster-RCTs

Where cluster-RCTs were included we planned to account for unit of analysis issues by data extracting a direct estimate of the required effect measure (for example, a RR with its CI) from an analysis that accounted for the cluster design properly (for example, an analysis based on a 'multilevel model', a 'variance components analysis' or that used 'generalised estimating equations (GEEs)'). Where these data were available we planned to use them in meta-analysis using the generic inverse-variance method (Deeks 2011). Where no such correct analysis of the cluster-randomised data were available, we planned to use approximate analyses using intracluster correlation co-efficient (ICC) analysis as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b, section 16.3.4). We did not identify any such cluster-randomised trials, so we did not need this methodology.

Dealing with missing data

We contacted (or attempted to contact) the authors of all potentially included RCTs to better assess inclusion. We contacted authors of all included trials that had randomised at least 100 participants (and some smaller trials) to request available data on all of the trial outcomes relevant to our set of reviews and key information on risk of bias. Due to limited resources, we focused on contacting authors of larger trials, who we thought were most likely to provide substantial quantities of useful data. We sent an email and a posted letter to the corresponding author at the latest address we were able to obtain (tracking latest publications in Medline). Where data on at least one review outcome were available (and at least one person had experienced a relevant outcome), we included the RCT, and asked the authors to provide any additional data about trial methodology or risk of bias.

Where papers reported continuous results as change from baseline we used these data, otherwise we used data at the latest point available. We did not impute change data.

Assessment of heterogeneity

We used the I^2 statistic (Higgins 2003) to measure heterogeneity among the trials in each analysis. Where we identified substantial heterogeneity (assumed when I^2 was greater than 50%, as 30% to 60% represents moderate heterogeneity and we were allowing for the varied dietary interventions included as well as potential dose effects) we reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

Where we were able to pool at least 10 trials, we created and examined a funnel plot to explore possible reporting biases for the primary outcomes (Sterne 2011).

We noted where we were aware of missing data. This occurred where trial methods noted that an outcome had been measured but those data had not been presented or had been presented but not by trial arm, where continuous data were unbalanced at baseline, or presented as medians or as means but without variance information.

Data synthesis

We undertook meta-analyses only where we considered it to be meaningful, that is, where the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. We carried out statistical analysis using RevMan 5 (RevMan 2014). We used a random-effects model, as dietary interventions are complex and somewhat heterogeneous by their nature (more so than most medical treatments), but we compared the results of random-effects and fixed-effect meta-analysis in sensitivity analyses. As the random-effects model assigns more weight to smaller trials, it is more conservative and may lead to imprecise estimates of effect. We also carried out sensitivity analyses to assess the effects of methodological rigour (see Sensitivity analysis).

'Summary of findings' table

We created a 'Summary of findings' table for the primary out-

- 1. all-cause mortality;
- 2. coronary heart disease events;
- 3. stroke; and
- 4. MACCEs.

As WHO NUGAG Subgroup on Diet and Health required a specific set of key outcomes for their guidance, we created a second 'Summary of findings' table for the key outcomes not represented in the main 'Summary of findings' table:

- 1. cardiovascular mortality;
- 2. cardiovascular events;
- 3. coronary heart disease mortality;
- 4. atrial fibrillation;
- 5. measures of adiposity body weight;
- 6. measures of adiposity BMI; and
- 7. serum lipids (including total cholesterol, fasting triglycerides, HDL and LDL).

We used the five GRADE considerations (trial limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it related to the trials that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 (Higgins 2011a) and Chapter 12 (Schünemann 2011) of the Cochrane Handbook for Systematic Reviews of Interventions, and used GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of trials using footnotes and made comments to aid reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We explored the effects of PUFA intake on primary outcomes and key outcomes by performing exploratory subgroup analyses on:

1. total PUFA dose (and dose response: total PUFA dose < 1% E, 1% E to < 2% E; 2% E to < 5% E and \geq 5% E where dose is

the difference in total PUFA intake between intervention and control arms);

- 2. trial duration: trials with medium follow-up (12 to 23 months), medium to long follow-up (24 to 47 months), and long follow-up (48 months or more);
- 3. baseline risk of cardiovascular disease (primary prevention, or secondary prevention);
- 4. baseline total PUFA intake (< 6% E from total PUFA, 6% E to < 11% E, and ≥ 11% E from total PUFA);
- 5. replacement of saturated fat, MUFA, carbohydrate and protein with total PUFA;
- 6. participants' sex (> 70% of the control group were men, > 70% of the control group were women, and mixed men and women);
- 7. participants' age (mean age in control group < 50 years, 50 to < 65 years and ≥ 65 years);
- 8. statin use (at least 50% of control group on statins versus fewer than 50% on statins); and
- 9. intervention type (dietary advice, supplements (capsules), supplemental foods and all foods provided, or any combination) We also planned to subgroup by change in the omega-3/omega-6 fat ratio (assessing whether the intervention primarily increased omega-3 fats (putting up the ratio) or omega-6 fats (lowering the ratio)). However, in almost no trials did we have information allowing us to calculate the omega-3/omega-6 fat ratio, so we did not carry out this subgrouping.

The 6% E and 11% E cut-offs for total PUFA were prespecified by WHO NUGAG Subgroup on Diet and Health, as their existing recommendations for PUFA intake were 6% E to 11% E in adults (WHO/FAO 2008).

We have not discussed differential effects of omega-3 and omega-6 PUFAs in this review, as separate reviews address the effects of omega-3 and omega-6 fats on cardiovascular disease in more detail (Hooper 2018; Abdelhamid 2018).

We used the formal test for subgroup interactions in RevMan 5 (RevMan 2014). These subgroupings were requested by WHO NUGAG Subgroup on Diet and Health to better help them understand the data. The danger of having so many subgroup analyses is that they may be over-interpreted, increasing the risk of a type one error.

Meta-regression

We planned meta-regression to further explore effects of total PUFA dose (looking for evidence of dose response), baseline total PUFA intake and duration on dichotomous primary and secondary outcomes with at least seven included trials and for which subgrouping was undertaken. However baseline total PUFA intake was only clear in a handful of trials, so we did not run meta-regression by baseline PUFA intake. Random-effects meta-regression (Berkley 1995) was performed using the STATA command metareg (Sharp 1998): log(e) relative risk versus [dose or primary/secondary prevention or type of intervention or risk of bias or du-

ration], weighted by the standard error of the log(e) relative risk. Where there were no events in one arm we added 0.1 to the numbers for both groups (so a trial with 10 people experiencing stroke in one arm but none in the other arm would be entered as 10.1 and 0.1).

Sensitivity analysis

We planned to carry out the following sensitivity analyses on all primary outcomes, and key outcomes:

- 1. only including trials with a low risk of bias for allocation concealment:
 - 2. only including trials with a low risk of attention bias;
- 3. only including trials with a low risk of bias from compliance;
 - 4. only including trials at low summary risk of bias;
- 5. only including all trials up to 2010, plus trials post-2010 that were registered in a trials register (Roberts 2015, regardless of the date of registration);
- 6. only including trials with no industry funding reported (trials with funding or support from partial bodies such as government boards to support specific foods or where funding was not mentioned were also excluded);
- 7. only including trials with less than 10% difference in intake of trans fats between trial arms during the intervention;
- 8. only including trials that randomised at least 100 participants;
- 9. only including trials that randomised at least 250 participants;
- 10. using fixed-effect meta-analysis.

Unfortunately almost no data on trans fats were available, so we did not carry out sensitivity analysis around trans fats.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included trials for this review. Outcome data were interpreted as follows:

- 1. Is there an effect? (Options were 'increased risk', 'decreased risk', or 'little or no effect'). Our main outcome measures were RR and MD so we decided on existence of an effect using RR. RR >8% (RR <0.92 or >1.08) for the highest quality evidence suggested increased or decreased risk (otherwise little or no effect). The presence or not of an effect was decided on the RR for the main analysis and sensitivity analyses.
- 2. Quality of evidence was assessed using GRADE assessment (GRADE Working Group 2004) for key outcomes. We used the

five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it related to the trials that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), plus GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of trials using footnotes and made comments to aid reader's understanding of the review.

3. Where there was a suggested effect the size of effect was assessed using the MD, NNT or ARR.

We avoided making recommendations for practice and our implications for research suggest priorities for future research and outline the remaining uncertainties in the area.

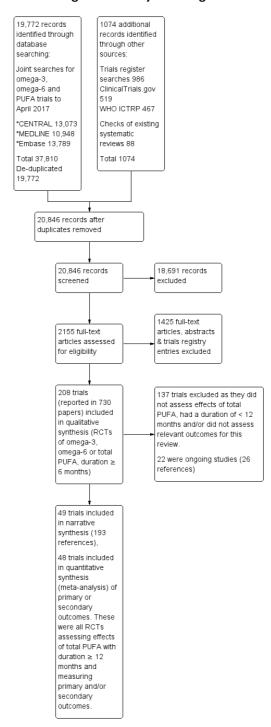
RESULTS

Description of studies

Results of the search

The electronic searches for the full set of reviews (populating the dataset of all trials that assessed effects of higher versus lower omega-6, omega-3 or PUFA over at least 6 months) generated 37,810 titles and abstracts, which we de-duplicated to 19,772 hits. We assessed these along with 53 studies previously included from Hooper 2018 and Abdelhamid 2018, to reassess for inclusion; 986 potentially relevant trials registry entries; and 35 new references gained from systematic review reference lists. In total, we assessed 20,846 titles and abstracts in duplicate to decide whether to retrieve full texts. We ultimately assessed 2155 full-text reports, of which 226 were systematic reviews. Two review authors independently assessed the remaining 1929 papers for inclusion and grouped them into studies. Of these, we included 208 RCTs in a wider set of trials that underpinned the full set of reviews (this review and several others including Abdelhamid 2018; Abdelhamid 2017; Hooper 2018; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Thorpe 2017). This wider set of trials included RCTs of omega-3, omega-6 or total polyunsaturated fatty acids (PUFA) interventions with a duration of at least six months (Figure 1) and comprised 730 reports.

Figure I. Study flow diagram



Of these 208 RCTs:

- 22 RCTs (26 documents) assessed effects of PUFA over at least one year but were ongoing (without published outcome data);
- 137 RCTs (361 documents) did not assess effects of a high enough dose of PUFA or had a duration of less than one year, so we excluded them; and
- 49 RCTs (183 documents) were eligible for inclusion in this review.

Of these 49 RCTs, 48 were included in meta-analyses. Details of the flow of trials are in Figure 1.

The 22 potential ongoing trials are described in the table of Characteristics of ongoing studies. These trials are very difficult to assess for inclusion in terms of total PUFA dose until further details are published. We will formally assess these trials for inclusion when we update this review.

Included studies

The details of the methods, participants, intervention, comparison group, and outcome measures for each of the included trials are shown in the Characteristics of included studies table. Forty-nine trials, including 24,272 randomised participants, met the inclusion criteria. Trials ranged in size from 36 randomised participants (Rossing 1996) to 4997 randomised participants (PREDIMED 2013), with 15 trials randomising at least 250 participants (AlphaOmega - ALA; Bates 1989; DART fat 1989; EPIC-1 2008; EPIC-2 2008; EPOCH 2011; FAAT - Leaf 2005; MRC 1968; NDHS Open 1st 1968; ORL 2013; PREDIMED 2013; Sydney Diet-Heart 1978; Veterans Admin 1969; WAHA - Ros 2016; WINS 2006).

Twenty-two trials recruited mostly men (at least 70% men in the control group, Ahn 2016; AlphaOmega - ALA; DART fat 1989; DIPP-Tokudome 2015; Doi 2014; Dullaart 1992; FAAT - Leaf 2005; GLAMT 1993; HARP- Sacks 1995; Kumar 2012; Ley 2004; Mendis 2001; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Nodari 2011 HF; Nye 1990; ORL 2013; Raitt 2005; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014), six trials recruited mostly women (at least 70% women in the control group, Bassey 2000-Post; Bassey 2000-Pre; Dodin 2005; Proudman 2015; Simon 1997; WINS 2006), 16 recruited similar numbers of men and women while five trials did not state the sex or participants (Bates 1977; EPOCH 2011; HERO-Tapsell 2009; McIllmurray 1987; Rose 1965).

Almost half of the trials (24 trials) recruited participants with a mean age between 50 and 65 years, but 12 trials recruited younger participants (mean age < 50 years, Bassey 2000-Pre; Bates 1978; Bates 1989; Dullaart 1992; EPIC-1 2008; EPIC-2 2008; NDHS Faribault 1968; NDHS Open 1st 1968; Puri 2005; Rossing 1996; Simon 1997; Sydney Diet-Heart 1978), eight trials recruited older

participants (mean age 65 years or more, AlphaOmega - ALA; Doi 2014; FAAT - Leaf 2005; Kumar 2013; Nodari 2011 AF; PREDIMED 2013; Veterans Admin 1969; WAHA - Ros 2016), and five trials did not give a mean age or range that could be classified (Ahn 2016; Bates 1977; EPOCH 2011; Houtsmuller 1979; Mendis 2001).

Twenty trials were conducted in Europe (AlphaOmega - ALA; Bassey 2000-Post; Bassey 2000-Pre; Bates 1977; Bates 1978; Bates 1989; Brox 2001; DART fat 1989; Dullaart 1992; GLAMT 1993; Houtsmuller 1979; MARINA - Sanders 2011; McIllmurray 1987; MRC 1968; Nodari 2011 AF; Nodari 2011 HF; PREDIMED 2013; Rose 1965; Rossing 1996; WELCOME 2015), 10 in North America (Black 1994; Dodin 2005; FAAT - Leaf 2005; HARP-Sacks 1995; NDHS Faribault 1968; NDHS Open 1st 1968; Raitt 2005; Simon 1997; Veterans Admin 1969; WINS 2006), seven in Asia (Ahn 2016; DIPP-Tokudome 2015; Doi 2014; Mendis 2001; Mita 2007; ORL 2013; Vijayakumar 2014), eight in Australia or New Zealand (EPOCH 2011; HERO-Tapsell 2009; Kumar 2012; Kumar 2013; Ley 2004; Nye 1990; Proudman 2015; Sydney Diet-Heart 1978), while four trials were conducted across several continents (EPIC-1 2008; EPIC-2 2008; Puri 2005; WAHA - Ros 2016).

The trials varied in the types of participants recruited and their level of cardiovascular risk. Most trials recruited participants without a personal history of cardiovascular disease (primary prevention), but 16 recruited participants with existing cardiovascular disease of some sort (secondary prevention of cardiovascular disease, Ahn 2016; AlphaOmega - ALA; DART fat 1989; Doi 2014; FAAT - Leaf 2005; HARP- Sacks 1995; Kumar 2012; Kumar 2013; MRC 1968; Nodari 2011 AF; Nodari 2011 HF; Nye 1990; Raitt 2005; Rose 1965; Sydney Diet-Heart 1978; Vijayakumar 2014).

Total PUFA dose (the difference in total PUFA between intervention and control arms) was between 0.6% E and less than 1% E for 13 trials (Doi 2014; EPOCH 2011; FAAT - Leaf 2005; Kumar 2012; Kumar 2013; Ley 2004; MARINA - Sanders 2011; Mita 2007; Nodari 2011 AF; Nodari 2011 HF; ORL 2013; Puri 2005; Raitt 2005), 1% E to less than 2% E total PUFA in 17 trials (Ahn 2016; AlphaOmega - ALA; Bassey 2000-Post; Bassey 2000-Pre; Bates 1977; Bates 1978; Bates 1989; Brox 2001; DIPP-Tokudome 2015; Dodin 2005; EPIC-1 2008; EPIC-2 2008; Nye 1990; PREDIMED 2013; Proudman 2015; WELCOME 2015; WINS 2006), 2% E to less than 5% E in eight trials (Black 1994; DART fat 1989; Dullaart 1992; GLAMT 1993; HARP- Sacks 1995; McIllmurray 1987; Mendis 2001; Rossing 1996), and at least 5% E from total PUFA in 11 trials (HERO-Tapsell 2009; Houtsmuller 1979; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Simon 1997; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014; WAHA - Ros 2016).

Increases in total PUFA were delivered to participants in various

ways. Most trials gave supplemental capsules or foods taken as supplements (supplemental oil drunk with meals in Rose 1965, seal or cod liver oil drunk in Brox 2001 and flax seed incorporated into foods in Dodin 2005), while eight trials gave dietary advice resulting in increased PUFA (Black 1994; DART fat 1989; Dullaart 1992; Houtsmuller 1979; Ley 2004; Simon 1997; Sydney Diet-Heart 1978; WINS 2006), eight trials gave supplemental foods such as margarines or nuts (AlphaOmega - ALA; HERO-Tapsell 2009; NDHS Faribault 1968; NDHS Open 1st 1968; PREDIMED 2013; Veterans Admin 1969; Vijayakumar 2014; WAHA - Ros 2016), and three trials used a combination of methods (DIPP-Tokudome 2015; Mendis 2001; MRC 1968). Baseline total PUFA intake was unclear in most trials, but where information was provided it ranged from 3.9% E (NDHS Open 1st 1968) to 8% E (Black 1994) in control groups. Seven trials had baseline total PUFA intake less than 6% E (Dodin 2005; HERO-Tapsell 2009; Ley 2004; NDHS Faribault 1968; NDHS Open 1st 1968; Veterans Admin 1969; WINS 2006), while nine had baselines of at least 6% E PUFA (Black 1994; DART fat 1989; DIPP-Tokudome 2015; Dullaart 1992; MARINA - Sanders 2011; PREDIMED 2013; Simon 1997; Sydney Diet-Heart 1978; WAHA - Ros 2016). PUFA replaced saturated fat at least partially in nine trials (DART fat 1989; Dullaart 1992; HARP- Sacks 1995; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014), replaced monounsaturated fats in 21 trials (AlphaOmega -ALA; Bates 1977; Bates 1978; Bates 1989; EPOCH 2011; FAAT - Leaf 2005; HARP- Sacks 1995; MARINA - Sanders 2011; NDHS Faribault 1968; NDHS Open 1st 1968; Nodari 2011 AF; Nodari 2011 HF; Nye 1990; PREDIMED 2013; Proudman 2015; Raitt 2005; Rose 1965; Rossing 1996; Sydney Diet-Heart 1978; Veterans Admin 1969; WELCOME 2015), replaced carbohydrate in 11 trials (Black 1994; DIPP-Tokudome 2015; Dodin 2005; Houtsmuller 1979; Ley 2004; MARINA - Sanders 2011; Mendis 2001; Rose 1965; Simon 1997; WAHA - Ros 2016; WINS 2006), and replaced protein at least partially in four trials (HERO-Tapsell 2009; Ley 2004; MRC 1968; WAHA - Ros 2016). In some trials PUFA replaced several dietary components, in others there was one main replacement, but replacements were unclear for 14 trials (Ahn 2016; Bassey 2000-Post; Bassey 2000-Pre; Brox 2001; Doi 2014; GLAMT 1993; Kumar 2012; Kumar 2013; EPIC-1 2008; EPIC-2 2008; McIllmurray 1987; Mita 2007; ORL 2013; Puri 2005).

In most trials fewer than 50% of participants in the control group were taking statins (assumed in trials published before 1994 when the 4S Trial 1994 was published showing overall benefits from statins in higher-risk populations and statin use began to rise, and in populations not at particular cardiovascular disease risk), but in seven trials at least 50% of participants were taking statins (Ahn 2016; AlphaOmega - ALA; Doi 2014; HERO-Tapsell 2009; Kumar 2013; Vijayakumar 2014; WELCOME 2015), and three trials were unclear (FAAT - Leaf 2005; Ley 2004; WAHA - Ros

2016).

The duration of the intervention was one to less than two years in most trials, but was two to less than four years in 16 trials (AlphaOmega - ALA; Bates 1977; Bates 1978; Bates 1989; Black 1994; DART fat 1989; DIPP-Tokudome 2015; Dullaart 1992; HARP- Sacks 1995; McIllmurray 1987; Mita 2007; Raitt 2005; Rose 1965; Simon 1997; Vijayakumar 2014; WAHA - Ros 2016), and four years or more in duration in six trials (Houtsmuller 1979; MRC 1968; PREDIMED 2013; Sydney Diet-Heart 1978; Veterans Admin 1969; WINS 2006).

Included trials were published over half a century between the 1960s (Rose 1965; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Veterans Admin 1969) and the 2010s (Ahn 2016; AlphaOmega - ALA; DIPP-Tokudome 2015; Doi 2014; EPOCH 2011; Kumar 2012; Kumar 2013; MARINA - Sanders 2011; Nodari 2011 AF; Nodari 2011 HF; ORL 2013; PREDIMED 2013; Proudman 2015; Vijayakumar 2014; WAHA - Ros 2016; WELCOME 2015), with some trials published in each decade. Funding sources were reported and appeared to be purely from national or charitable agencies in 17 trials (Ahn 2016; Black 1994; Brox 2001; DIPP-Tokudome 2015; Dullaart 1992; FAAT - Leaf 2005; Houtsmuller 1979; Ley 2004; MARINA - Sanders 2011; Mendis 2001; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Nodari 2011 AF; Sydney Diet-Heart 1978; Vijayakumar 2014; WINS 2006). Seven trials appeared to be directly funded by industrial sources (Bassey 2000-Post; Bassey 2000-Pre; EPIC-1 2008; EPIC-2 2008; GLAMT 1993; ORL 2013; Puri 2005), two funded by bodies set up to promote specific foods (HERO-Tapsell 2009; WAHA - Ros 2016), 16 trials funded by some governmental or charity sources with additional funding or support from commercial sources (AlphaOmega - ALA; Bates 1977; Bates 1978; Bates 1989; DART fat 1989; EPOCH 2011; HARP- Sacks 1995; Kumar 2012; Nye 1990; PREDIMED 2013; Proudman 2015; Raitt 2005; Rossing 1996; Simon 1997; Veterans Admin 1969; WELCOME 2015), two trials that included authors on industry honoraria (Doi 2014; Nodari 2011 HF), and five trials where funding was not reported (Dodin 2005; Kumar 2013; McIllmurray 1987; Mita 2007; Rose 1965).

Most included trials had a single intervention arm and a single control arm, but some trials were more complex.

- 1. Bates 1977 had four arms, two intervention arms each had their own control arm, so were dealt with as separate trials. Both were included, as deaths appear to have occurred, but it is no longer clear how many or which arms they occurred in.
- 2. Bates 1978 also had two intervention arms each with their own control arm, but comparison C versus D did not have any relevant outcome data so we excluded it. We only included A versus B.
- 3. Brox 2001 had two intervention arms and one control arm. For all outcomes, we combined the two intervention groups and compared to the single control group.
- 4. DART fat 1989 was a factorial trial, but we have included

only one of the three factorial interventions in this review, so all participants have been included only once.

- 5. MARINA Sanders 2011 had three intervention arms of different doses and one control arm. Only one intervention arm was included in this review (D2) and compared to the control arm.
- 6. NDHS Faribault 1968 and NDHS Open 1st 1968 each had three intervention arms and a single control. We combined data for the three arms and compared them to the single control arm in each trial.
- 7. Nye 1990 had three arms, but one was irrelevant to this review so not included.
- 8. ORL 2013 had three arms, but we only included two arms (higher vs lower dose omega-3)
- 9. PREDIMED 2013 had three arms, a Mediterranean diet with nuts, a Mediterranean diet with olive oil and a low-fat arm. For this review we compared the Mediterranean diet with nuts (high PUFA) with the Mediterranean diet with olive oil (low PUFA) as these two arms were very similar but with different PUFA intakes. For many outcomes data were reported in publications by trial centre (or combination of trial centres), so we checked for overlap of participants then reported the

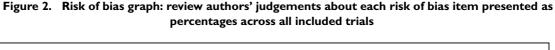
outcome centre by centre where we were sure that no participants were included more than once.

Excluded studies

We have presented details and reasons for exclusion of the trials that most closely missed the inclusion criteria in the Characteristics of excluded studies table.

Risk of bias in included studies

Our assessment of risk of bias of included trials is summarised in Figure 2 and detailed by trial in Figure 3. We assessed eleven of the 49 included trials as being at low summary risk of bias; eight trials as being at low risk of bias from randomisation, allocation concealment, performance and detection biases (AlphaOmega - ALA; EPOCH 2011; MARINA - Sanders 2011; NDHS Faribault 1968; NDHS Open 1st 1968; Proudman 2015; Puri 2005; WELCOME 2015), and three trials, which were dietary advice or provision trials, as being at low risk of bias from randomisation, allocation concealment and detection bias (Ley 2004; Sydney Diet-Heart 1978; WINS 2006). We assessed the remaining 37 trials as being at moderate or high risk of bias.



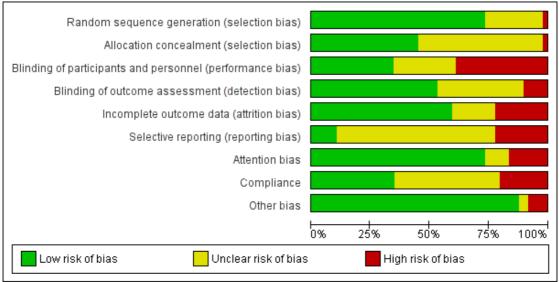
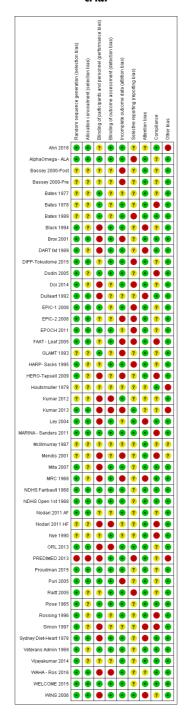


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial



Allocation

Randomisation was adequate in 36 of the 49 trials, not well described in 12 trials and at high risk in one trial (PREDIMED 2013). Allocation concealment was appropriate in 22 included trials, unclear in 26, and at high risk of bias in one (PREDIMED 2013). Twenty-two trials were at low risk of selection bias, with low risk of bias from both randomisation and allocation concealment (see Figure 3).

Blinding

Blinding of participants and personnel appeared at low risk of bias for 17 trials, unclear for 13 and at high risk of bias for the remaining 19 trials. Blinding of outcome assessors was at low risk of bias in 26 trials, unclear in 18 and at high risk of bias in five trials. Eleven trials were well blinded, at low risk of bias from both blinding of participants, personnel and outcome assessors.

Incomplete outcome data

Twenty-nine trials appeared to be at low risk of attrition bias, 11 were at high risk and the remainder unclear.

Selective reporting

We found five trials that had a trials registry entry or protocol published before data collection was completed, and reported all outcomes suggested in the entry or protocol. Thirty-three were unclear, generally because no trials registry entry or protocol was identified, or because they were published after the end of data collection. We found 11 trials were at high risk of selective reporting, as at least one outcome suggested in the trials registry entry or protocol was not reported in full.

We attempted to access additional outcome data as well as methodological data from most included trials. We established contact with most trial authors, and received data on outcomes that had not been fully published from many (noted in Characteristics of included studies for relevant trials), although some trial authors were unable to provide additional information or repeated phrases from their published papers. We tried to contact, but did not receive any reply from, authors of 10 trials (Ahn 2016; Doi 2014; GLAMT 1993; Houtsmuller 1979; Kumar 2012; Kumar 2013; Mendis 2001; Nodari 2011 AF; ORL 2013; Raitt 2005). We did not attempt to contact authors of some of the oldest trials, as the trials were conducted in the 1960s and their authors were unlikely to be accessible (NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Veterans Admin 1969), although we had made contact with the retired statistician of another older trial when including that trial in an earlier systematic review (MRC 1968). We did not

attempt to contact authors of five trials (Bassey 2000-Post; Bassey 2000-Pre; HERO-Tapsell 2009; Mita 2007; Nye 1990).

Other potential sources of bias

We assessed attention bias, where intervention participants appeared to receive more time or attention from health professionals than those in the control group. Thirty-six trials appeared to be at low risk of attention bias, eight were at high risk, and the remaining five were unclear.

We assessed compliance, to ensure that PUFA truly appeared to have been higher in one arm than the other, by looking for evidence of changes or differences in a body biomarker (total PUFA had to be assessed by at least linoleic acid (LA) plus one or more further components of PUFA), or greater reduction in total cholesterol in the higher PUFA arm. Where lipid biomarker and total cholesterol contradicted each other we chose unclear. We found that 17 trials demonstrated appropriate compliance, 10 suggested poor compliance while 22 trials were unclear.

Four trials were found to be at high risk from other potential bias. Ahn 2016 was unclear about whether the control arm received a placebo or not, and some SDs appeared to be incorrectly reported. When we looked for additional data on Houtsmuller 1979 we found that concerns had been raised over potential research fraud of the first author in later trials (assessing effects of diet on cancer). While no concerns were found about the included research we felt that this did potentially reflect a risk of fraud in the included trial. In Kumar 2013, 21 of the 39 participants randomised to the intervention were inexplicably crossed over to the control condition at six months, so that 12-month outcomes were only reported for 17 of the 39 randomised participants. The main publication of PREDIMED 2013 was retracted and republished in 2018 due to randomisation and allocation concealment problems not mentioned in the initial publication that resulted in a distribution of baseline variables inconsistent with randomisation (Carlisle 2017). We found McIllmurray 1987 and Mendis 2001 to be at unclear risk of other bias, as neither described their control group interventions. The remaining trials were considered to be at low risk of other potential bias.

Effects of interventions

See: Summary of findings for the main comparison Higher polyunsaturated fatty acid (PUFA) compared to lower PUFA for cardiovascular disease - primary outcomes; Summary of findings 2 Higher polyunsaturated fatty acid (PUFA) compared to lower PUFA for cardiovascular disease - additional key outcomes

Primary outcomes

For 'Summary of findings' table on primary outcomes see Summary of findings for the main comparison.

All-cause mortality

PUFA intake probably has little or no effect on all-cause mortality (moderate-quality evidence).

Twenty-four trials including 19,290 participants reported at least one death and could be added to the meta-analysis. There was no clear effect of more PUFA compared to less PUFA intake on allcause mortality (RR 0.98, 95% CI 0.89 to 1.07, $I^2 = 0\%$, 1443 deaths; Analysis 1.1). This lack of effect did not differ in fixedeffect analysis (RR 0.98, 95% CI 0.89 to 1.07; Analysis 1.3), or sensitivity analysis restricting to trials at low risk of bias for allocation concealment (RR 1.03, 95% CI 0.87 to 1.22), low risk of attention bias (RR 0.96, 95% CI 0.87 to 1.07), compliance bias (RR 1.01, 95% CI 0.89 to 1.14), low summary risk of bias (RR 1.04, 95% CI 0.87 to 1.26), trials registry or pre-2010 publication (RR 0.99, 95% CI 0.90 to 1.08), trials without any industry funding (RR 1.09, 95% CI 0.84 to 1.42), that randomised at least 100 participants (RR 0.98, 95% CI 0.89 to 1.08) or at least 250 participants (RR 1.00, 95% CI 0.91 to 1.10; Analysis 1.2). The funnel plot did not suggest any publication bias, though we are aware of two trials with deaths that we were not able to add to the analyses (Bates 1977; Simon 1997).

Subgrouping did not suggest differential effects by total PUFA dose (Analysis 1.4), duration (Analysis 1.5), primary or secondary prevention (Analysis 1.6), baseline PUFA intake (Analysis 1.7), dietary component displaced by the increase in PUFA (Analysis 1.8), participant sex (Analysis 1.9), participant age (Analysis 1.10), statin use (Analysis 1.11), or type of intervention (Analysis 1.12). There was no suggestion of important effects in any of the four trials each taking more than 10% of the weight in meta-analysis (AlphaOmega - ALA; DART fat 1989; PREDIMED 2013; Veterans Admin 1969).

Meta-regression did not suggest any relationships between total PUFA dose (P = 0.94) or trial duration (P = 0.81) and all-cause mortality. We did not run meta-regression of baseline PUFA dose and all-cause mortality as few trials provided this information. We downgraded the GRADE evidence level for imprecision as the 95% CI included important benefits (moderate-quality evidence), Summary of findings for the main comparison.

Coronary heart disease events

PUFA intake probably reduces risk of coronary heart disease events slightly (NNT 53, moderate-quality evidence).

Fifteen trials including 10,076 participants were included and 1351 participants reported at least one coronary heart disease event. Meta-analysis suggested that higher PUFA intake resulted in 13% fewer participants having coronary heart disease events

(RR 0.87, 95% CI 0.72 to 1.06, I^2 = 45%; Analysis 1.13). None of the four trials that carried at least 10% of the weight of the meta-analyses suggested statistically significant effects in their own right (AlphaOmega - ALA; DART fat 1989; MRC 1968; Veterans Admin 1969). The funnel plot did not suggest any serious publication bias (not shown).

Sensitivity analyses using fixed-effects analysis suggested a 10% reduction in risk of coronary heart disease with increased PUFA (RR 0.90, 95% CI 0.82 to 0.99; Analysis 1.15), but other sensitivity analyses suggested varying results both sides of no effect (RR 1.00). These included restricting to trials at low risk of bias for allocation concealment (RR 1.14, 95% CI 0.73 to 1.78), low risk of attention bias (RR 0.86, 95% CI 0.72 to 1.02), compliance bias (RR 0.87, 95% CI 0.65 to 1.17), low summary risk of bias (RR 1.18, 95% CI 0.76 to 1.81), trials registry or pre-2010 publication (RR 0.87, 95% CI 0.72 to 1.06), trials without any industry funding (RR 0.72, 95% CI 0.31 to 1.63), that randomised at least 100 participants (RR 0.87, 95% CI 0.70 to 1.08) or at least 250 participants (RR 0.94, 95% CI 0.82 to 1.09; Analysis 1.14).

Subgrouping by PUFA dose and trial duration did not suggest important differences between subgroups, or dose or duration effects. There were only six events in trials with doses of less than 1% E (Analysis 1.16) and 21 events in trials of less than two years (Analysis 1.17). Meta-regression did not suggest any relationship between PUFA dose (P = 0.69) or trial duration (P = 0.51) and coronary heart disease events.

Subgrouping did not suggest differential effects by primary or secondary prevention (P = 0.12; Analysis 1.18), baseline PUFA intake (Analysis 1.19), replacement of saturated fat or MUFA with PUFA (Analysis 1.20), age (Analysis 1.22), statin use or intervention type (Analysis 1.23; Analysis 1.24). Most coronary heart disease events occurred in trials of men, there is insufficient information to understand effects in other subgroups, though rather surprisingly there was a significant difference between subgroups of men and women combined and trials of mostly men or mostly women (Analysis 1.21).

We downgraded the GRADE evidence level for imprecision and risk of bias combined (as despite over 10,000 participants the 95% confidence intervals included harm from increasing PUFA as well as benefit). PUFA intake probably reduces risk of coronary heart disease events, from 14.2% to 12.3% in the study populations, NNT 53 (moderate-quality evidence), Summary of findings for the main comparison.

Stroke

PUFA intake may very slightly reduce risk of stroke (NNT 1000, low-quality evidence). However, the 95% confidence intervals include important harms as well as benefit.

Eleven trials including 14,742 participants of whom 166 experienced at least one fatal or non-fatal stroke. Meta-analysis suggested some reduction in risk of stroke with increased PUFA, but

confidence intervals were wide (RR 0.91, 95% CI 0.58 to 1.44, $I^2 = 24\%$; Analysis 1.25). The funnel plot did not suggest any small study bias (not shown).

This suggestion of benefit from PUFA was also seen in the fixed-effect sensitivity analysis (RR 0.82, 95% CI 0.61 to 1.11, Analysis 1.27). While sensitivity analyses retaining only trials at low risk of bias from allocation concealment, attention and low summary risk of bias all suggested reduced stroke risk with increased PUFA, as did those on trials registers or pre-2010, and trials of at least 100 participants, this was not the case for sensitivity analyses of trials at low risk of bias from compliance (RR 1.36, 95% CI 0.45 to 4.11, $I^2 = 56\%$), trials without industry funding or of at least 250 participants (RR 0.98, 95% CI 0.60 to 1.60, $I^2 = 33\%$), Analysis 1.26.

Subgrouping did not suggest greater effects with higher doses of PUFA (Analysis 1.28), or longer duration (Analysis 1.29), without significant differences between subgroups. Meta-regression did not suggest relationships between PUFA dose and stroke (P = 0.69), but there was limited non-statistically significant suggestion of greater benefit in longer trials (P = 0.11).

There were no significant differences between subgroups by primary or secondary prevention (P = 0.20; Analysis 1.30), baseline PUFA dose (Analysis 1.31), sex (Analysis 1.33), statin use (Analysis 1.35), fatal or non-fatal stroke (Analysis 1.37), replacement (Analysis 1.32), or intervention type (Analysis 1.36). There were differences when subgrouping was by age (Analysis 1.34), but greater protection at older age was balanced by harm in midlife - a confusing picture. Where data on ischaemic or haemorrhagic stroke could be separated out, both subgroups suggested harm from increased PUFA, while data on combined ischaemic and haemorrhagic events suggested benefit from increased PUFA, again a non-intuitive pattern (Analysis 1.38).

We downgraded the GRADE quality assessment twice for imprecision (even though over 14,000 participants were included only 166 people experienced stroke so we were underpowered to assess effects). PUFA intake may reduce risk of stroke, from 1.2% to 1.1% in the study populations, NNT 1000 (low-quality evidence), but harms are not ruled out, Summary of findings for the main comparison.

Major adverse cardiac and cardiovascular events (MACCEs)

Effects of PUFA on risk of MACCEs are unclear as data are of very low quality.

Two trials recruited 1879 participants, and 817 people experienced at least one MACCE. The trials suggested a 16% decrease in MACCE risk with increased PUFA, but were highly heterogeneous (RR 0.84, 95% CI 0.59 to 1.20, $I^2 = 79\%$; Analysis 1.39). With only two included trials assessment of small study bias was not possible, and fixed-effect analysis also suggested some benefit of PUFA (RR 0.92, 95% CI 0.82 to 1.04, $I^2 = 79\%$; Analysis 1.41). Most sensitivity analyses preserved the suggested reduction

of risk of MACCEs with increased PUFA but no trials were at low summary risk of bias and none were at low risk of bias from allocation concealment (Analysis 1.40).

With only two trials, subgrouping was generally uninformative (Analysis 1.42; Analysis 1.43; Analysis 1.44; Analysis 1.45; Analysis 1.46; Analysis 1.47; Analysis 1.48; Analysis 1.49; Analysis 1.50). Whenever the two trials were in separate subgroups there was a statistically significant difference between subgroups. We did not attempt meta-regression.

We downgraded GRADE assessment for risk of bias, inconsistency and imprecision. Effects of PUFA on risk of MACCEs was unclear as data are of very low quality, Summary of findings for the main comparison.

Secondary outcomes

We formally systematically reviews secondary outcomes, in that we included all relevant trials that collected data on any of these outcomes. Summary of findings 2 displays GRADE assessments for the key outcomes not included in this review's primary outcomes.

Cardiovascular mortality

Increasing PUFA intake may have little or no effect on cardiovascular mortality (low-quality evidence).

Sixteen trials randomising 15,107 participants of whom 729 died of cardiovascular causes were included. Meta-analysis suggested little effect of PUFA intake on cardiovascular disease deaths (RR 1.02, 95% CI 0.82 to 1.26, I² = 31%; Analysis 2.1). Sensitivity analyses suggested small non-significant benefits (limiting to trials at low risk of bias for attention) or non-significant harms (limiting to trials at low risk of bias for allocation concealment, compliance, summary risk of bias, trials registry entry or pre-2010, no industry funding, and larger trials; Analysis 2.2), and fixed-effect analysis suggested no effect (RR 1.01, 95% CI 0.88 to 1.16; Analysis 2.3). The funnel plot suggested that one or two smaller trials with RRs greater than 1.00 might be missing - replacing these would tend to raise the RR, suggesting slight harm.

Subgrouping by PUFA dose suggested no statistically significant subgroup differences (Analysis 2.4). Meta-regression did not suggest any relationship with dose (P = 0.54). Subgrouping by duration showed no important differences between subgroups (P = 0.72; Analysis 2.5). Meta-regression on duration was not statistically significant (P = 0.11).

Subgrouping by primary or secondary prevention, replacement, sex, statin use, and intervention type did not explain any of the heterogeneity and subgroups did not differ significantly (Analysis 2.6; Analysis 2.8; Analysis 2.9; Analysis 2.11; Analysis 2.12). Subgrouping by baseline PUFA intake included six trials and suggested benefit of increasing PUFA intake in groups with baseline total PUFA intake less than 6% E (RR 0.71, 95% CI 0.52 to 0.97, I² =

0%, 141 cardiovascular disease deaths), but harm in groups with higher baseline PUFA intake (RR 1.32, 95% CI 1.07 to 1.62, I² = 0%, 326 cardiovascular disease deaths), removing heterogeneity and suggesting a statistically significant test for subgroup differences (P = 0.003; Analysis 2.7). Subgrouping by participant age also reduced heterogeneity and suggested significant subgroup differences (P = 0.02; Analysis 2.10), suggesting harm from additional PUFA in adults aged under 50 years, more modest harm in those aged 50 to 65 years, and benefit in those aged at least 65 years. These data could suggest greater utility of increasing total PUFA when baseline intake is low, and in older adults, but given the small number of trials caution is appropriate.

We downgraded the GRADE assessment twice for imprecision (as important benefits and harms were included in the 95% confidence intervals). Increasing PUFA intake may have little or no effect on cardiovascular mortality (low-quality evidence).

Cardiovascular events

Increasing PUFA intake probably reduces risk of cardiovascular events a little (NNT 59, moderate-quality evidence).

Twenty trials randomising 17,799 participants reported at least one cardiovascular event in 2442 participants. Meta-analysis suggested that increasing total PUFA intake reduced the risk of cardiovascular disease events by 11%, with little heterogeneity (RR 0.89, 95% CI 0.79 to 1.01, I² = 30%; Analysis 2.13), as did fixed-effect analysis (RR 0.92, 95% CI 0.86 to 0.98; Analysis 2.15). Sensitivity analyses limiting to trials with low risk of bias from attention bias, trials registry entry or pre-2010, trials with at least 100 or at least 250 participants all retained suggestion of benefit from increased PUFA, while sensitivity analyses for allocation concealment, compliance, and industry funding suggested no important effects, and limiting to studies with low summary risk of bias suggested increased risk (Analysis 2.14). The funnel plot did not suggest small study bias (not shown).

Subgrouping by PUFA dose and trial duration did not show statistically significant differences between subgroups (P = 0.17 and 0.18 respectively; Analysis 2.16; Analysis 2.17). Meta-regression

did not suggest relationships between cardiovascular disease events and PUFA dose (P = 0.78) or trial duration (P = 0.70).

Subgrouping by primary or secondary prevention, baseline PUFA dose, replacement, sex, statin use, and intervention type did not reduce heterogeneity and did not suggest significant differences between subgroups (Analysis 2.18; Analysis 2.19; Analysis 2.20; Analysis 2.21; Analysis 2.23; Analysis 2.24). Subgrouping by participant age suggested harm in younger participants (RR 1.66, 95% CI 1.05 to 2.61, $I^2=0\%$), but benefit in middle-aged and older participants (RR 0.86, 95% CI 0.78 to 0.96, $I^2=0\%$), with statistically significant differences between subgroups (P = 0.03; Analysis 2.22).

We downgraded the GRADE assessment for risk of bias (as sensitivity analyses suggested benefit, no effect and some harm from increased PUFA). Increasing PUFA intake probably reduces risk of cardiovascular events from 14.6% to 13.0% in study populations, NNT 63 (moderate-quality evidence).

Coronary heart disease mortality

Increasing PUFA intake may reduce risk of coronary heart disease death by a small amount (NNT 200, low-quality evidence). Nine trials randomised 8810 participants of whom 556 died of coronary heart disease. Meta-analysis suggested that increasing PUFA intake reduced risk of coronary heart disease death, without heterogeneity (RR 0.91, 95% CI 0.78 to 1.06, I² = 0%; Analysis 2.25). Results from the fixed-effect analysis were very similar (RR 0.90, 95% CI 0.77 to $1.05, I^2 = 0\%$; Analysis 2.27). Although nine trials provided data, of the 556 deaths, 340 occurred in DART fat 1989, which carried 65% of the weight of the meta-analysis, and 138 occurred in AlphaOmega - ALA, which carried 23% of the weight. Results of all the sensitivity analyses were similar, all suggesting modest protection from increased PUFA (Analysis 2.26), although no subgroups were statistically significant. The funnel plot suggested that some small trials with RR over 1.0 may be missing, and if these trials were added back in they would tend to raise the RR towards 1.0 (Figure 4).

Figure 4. Funnel plot of comparison 2. Higher PUFA vs lower PUFA - dichotomous secondary outcomes, outcome: 2.25 CORONARY HEART DISEASE (CHD) MORTALITY

Subgrouping by dose and duration did not suggest subgroup differences (P=0.92 and 0.90 respectively), though there was a counter-intuitive suggestion that lower doses and shorter durations produced greater benefits (Analysis 2.28; Analysis 2.29). Meta-regression did not suggest strong relationships between PUFA dose (P=0.62) or trial duration (P=0.71) and risk of coronary heart disease death.

0.1

Subgrouping by primary or secondary cardiovascular disease prevention, baseline PUFA dose, replacement, sex, age, statin use, or intervention type did not suggest important differences between subgroups (Analysis 2.30; Analysis 2.31; Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35; Analysis 2.36).

We downgraded the GRADE assessment for imprecision and publication bias. Increasing PUFA intake may reduce risk of coronary heart disease death a little from 6.6% to 6.1% in the study populations, NNT 200 (low-quality evidence).

Myocardial infarction

2+ 0.01

Increasing PUFA may reduce risk of myocardial infarction. Fifteen trials randomising 15,609 participants recorded 880 myocardial infarctions. Meta-analysis suggested that increasing PUFA reduced the risk of myocardial infarction by 12% without hetero-

geneity (RR 0.88, 95% CI 0.78 to 0.99, $I^2 = 0\%$; Analysis 2.37). We did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome.

100

Sudden cardiac death

The effect of increasing PUFA on sudden cardiac death is unclear. Five trials recruited 1731 participants of whom 69 experienced sudden cardiac death. Meta-analysis suggested some benefit from increasing PUFA (RR 0.80, 95% CI 0.50 to 1.29, I^2 = 0%; Analysis 2.38), but the effect was not statistically significant, and did not exclude important harms. There were insufficient trials to assess the funnel plot. We did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome.

Atrial fibrillation

The effect of increasing PUFA intake on atrial fibrillation is unclear as the evidence is of very low quality.

Eleven trials recruited 11,692 participants of whom 811 experienced new or recurrent atrial fibrillation. Meta-analysis suggested that increasing PUFA reduced the risk of atrial fibrillation by 13%

with substantial heterogeneity (RR 0.87, 95% CI 0.72 to 1.06, I ² = 57%, Analysis 2.39). Fixed-effect analysis suggested marginal statistical significance (RR 0.87, 95% CI 0.72 to 1.06, $I^2 = 57\%$; Analysis 2.39). Sensitivity analyses generally suggested a non-significant protective effect of the trials at lower risk of bias, but trials without industry funding and those at low risk from allocation concealment suggested a statistically significant reduction(Analysis 2.40). No trials were at low risk of bias from compliance problems. Subgrouping by new or recurrent atrial fibrillation suggested no important differences between subgroups (P = 0.31; Analysis 2.39). Subgrouping by PUFA dose did not suggest important differences between subgroups (Analysis 2.42), but subgrouping by duration suggested greater protection in shorter trials (P = 0.001; Analysis 2.43). Meta-regression suggested that there was no relationship between PUFA dose and atrial fibrillation (P = 0.91), but there was a marginally significant relationship between duration and risk of atrial fibrillation (with benefit in shorter trials and harm in longer trials, P = 0.056).

Subgrouping suggested no important effects by replacement, sex, age, intervention type or statin use (no subgroup differences; Analysis 2.46; Analysis 2.47; Analysis 2.48; Analysis 2.49; Analysis 2.50). Subgrouping suggested that PUFA was harmful in primary prevention (RR 1.33, 95% CI 0.99 to 1.79, I^2 = 0%) and beneficial in secondary prevention of cardiovascular disease (RR 0.80, 95% CI 0.67 to 0.96, I^2 = 58%), with significant subgroup differences (P = 0.004; Analysis 2.44). Only one trial had a known baseline PUFA intake so subgrouping was unhelpful (Analysis 2.45).

We downgraded the GRADE assessment for risk of bias, inconsistency and imprecision. The effect of increasing PUFA intake on atrial fibrillation is unclear as the evidence is of very low quality.

Angina

The effect of increasing PUFA intake on angina is unclear. Seven trials including 2070 participants reported 100 participants experiencing new or worsening angina. Meta-analysis suggested that increasing PUFA reduced risk of angina (RR 0.64, 95% CI 0.35 to 1.16, I² = 46%; Analysis 2.51). There were insufficient trials to assess the funnel plot and we did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome. One included trial had adequate allocation concealment and none were at low summary risk of bias.

Heart failure

The effect of increasing PUFA intake on heart failure is unclear. Seven trials including 25,257 participants reported 137 participants experiencing new or worsening heart failure. Meta-analysis suggested that increasing PUFA reduced risk of heart failure but results were heterogeneous and important harms were not excluded (RR 0.74, 95% CI 0.40 to 1.36, I^2 = 54%; Analysis 2.52). There were insufficient trials to assess the funnel plot and we did not

plan to carry out sensitivity analyses, subgroup analyses or metaregression for this outcome. Two included trials had adequate allocation concealment and one was at low summary risk of bias.

Peripheral arterial disease

Increasing PUFA intake may increase the risk of peripheral arterial disease.

Four trials including 8937 participants reported 97 participants experiencing new or worsening peripheral arterial disease. Meta-analysis suggested that increasing PUFA increased risk of peripheral arterial disease but important benefits were not excluded (RR 1.20, 95% CI 0.81 to 1.77, $I^2 = 0\%$; Analysis 2.53). There were insufficient trials to assess the funnel plot and we did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome. Two included trials had adequate allocation concealment and two were at low summary risk of bias.

Revascularisation

The effect of increasing PUFA intake on revascularisation is unclear.

Six trials including 1182 participants reported 46 participants undergoing revascularisation. Meta-analysis suggested that increasing PUFA reduced risk of revascularisation but important harms were not excluded (RR 0.70, 95% CI 0.40 to 1.24, $I^2 = 0\%$; Analysis 2.54). There were insufficient trials to assess the funnel plot and we did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome. One included trial had adequate allocation concealment and one was at low summary risk of bias.

Adiposity - body weight

Higher PUFA intake probably results in greater weight gain (moderate-quality evidence).

Twelve trials presenting 15 comparisons, of which 13 could be included in meta-analyses, included 7100 participants with data on body weight. Meta-analyses suggested that weight increased with increased PUFA intake, although trials were heterogeneous (MD 0.76 kg, 95% CI 0.34 to 1.19, $I^2 = 59\%$; Analysis 3.1). The funnel plot suggested that some trials with smaller weight increases or reductions in the increased PUFA group may be missing. If replaced, these trials would tend to reduce the weight increase in the higher PUFA participants. Two trials (both also suggesting increased weight in the higher PUFA arm) did not provide variance data so could not be included in the meta-analysis, though they are shown in the forest plot (Analysis 3.1). A further five trials collected data on weight but did not provide those data in a way that could be included in meta-analysis (MARINA - Sanders 2011; NDHS Faribault 1968; NDHS Open 1st 1968; Simon 1997; Vijayakumar 2014).

The effect was larger when we used fixed-effect analysis (MD 1.08 kg, 95% CI 0.96 to 1.21; Analysis 3.3). Sensitivity analyses all suggested increased body weight with increased PUFA intake (although not statistically significantly when we limited to trials at low risk of compliance bias, Analysis 3.2).

Subgrouping by PUFA dose, duration, primary or secondary prevention, replacement, sex, age and statin use did not differ significantly by subgroups (Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.8; Analysis 3.9; Analysis 3.10; Analysis 3.11). There were important differences between subgroups when grouping by baseline PUFA dose, with greater weight increases for those with lower baseline PUFA intake (Analysis 3.7). Subgrouping by intervention type suggested differences between subgroups (P = 0.01; Analysis 3.12), suggesting greater weight increases with increased PUFA intake by dietary advice (MD 2.37 kg, 95% CI 1.19 to 3.55, $I^2 = 0\%$) than in trials of supplemental foods or diet provided (MD 0.71 kg, 95% CI 0.18 to 1.25, $I^2 = 73\%$), or in supplemental trials (MD 0.37 kg, 95% CI -0.18 to 0.91, $I^2 = 0\%$). We downgraded the GRADE assessment of evidence for publication bias, leading to a moderate quality of evidence. Higher PUFA intake probably results in greater weight gain.

Adiposity - BMI

Higher PUFA intake may lead to higher BMI (low-quality evidence).

Eight trials reported 11 comparisons including 4798 participants with BMI reported. Meta-analysis suggested that increasing PUFA intake results in greater BMI, but effects were heterogeneous (MD 0.17 kg/m², 95% CI -0.08 to 0.42, $I^2 = 80\%$, Analysis 3.13). Fixed-effect analysis was statistically significant (MD 0.27 kg/m², 95% CI 0.20 to 0.35, $I^2 = 80\%$; Analysis 3.15). The funnel plot did not suggest any small study bias, and we are aware of two trials that assessed BMI but did not provide data that could be used in meta-analysis (Simon 1997; Vijayakumar 2014). Sensitivity analyses all confirmed slightly increased BMI with increased PUFA intake (Analysis 3.14).

Subgrouping by PUFA dose, duration, primary or secondary prevention, baseline PUFA intake, replacement, sex, age, statin use and intervention type did not suggest important differences between subgroups (Analysis 3.16; Analysis 3.17; Analysis 3.18; Analysis 3.19; Analysis 3.20; Analysis 3.21; Analysis 3.22; Analysis 3.23; Analysis 3.24), and did not reduce heterogeneity.

We downgraded the GRADE assessment for inconsistency and imprecision, leading to low-quality evidence. Higher PUFA intake may lead to higher BMI.

Adiposity - other measures

Several trials reported waist circumference (1298 participants in two trials; Analysis 3.25), percentage body fat (309 participants in two trials; Analysis 3.26) and body fat in kg (214 participants in a

single trial; Analysis 3.27). Meta-analyses on waist circumference and percentage body fat both suggested greater weight gain in those on higher PUFA intake, while the single trial with data on body fat in kg suggested no difference in body fat regardless of PUFA intake. We are aware of several trials that assessed adiposity but did not provide data in a format that could be included in meta-analysis. HERO-Tapsell 2009 and Simon 1997 assessed percentage of body fat, and WAHA - Ros 2016 assessed waist circumference (shown in the meta-analysis but without variance data).

Lipids - serum total cholesterol

Higher PUFA intake leads to lower total cholesterol (high-quality evidence).

Twenty six trials, incorporating data from 8072 participants (and 28 trial arms), provided data on serum total cholesterol. Meta-analysis suggested that increasing PUFA intake reduced total cholesterol, although data were heterogeneous (MD -0.12 mmol/L, 95% CI -0.23 to -0.02, I^2 = 79%; Analysis 3.28). The funnel plot was difficult to interpret, but we were aware of one trial (MRC 1968) that provided total cholesterol data without variance information, so could not be included in meta-analysis. This trial also suggested reduced total cholesterol in the higher PUFA arm (Analysis 3.28). Total cholesterol data from five trials (Dullaart 1992; EPOCH 2011; ORL 2013; Veterans Admin 1969; WINS 2006) could not be included in meta-analysis, so are missing.

Sensitivity analyses, including fixed-effect analysis, all suggested greater total cholesterol reduction with higher PUFA intake, although some were not statistically significant (Analysis 3.29; Analysis 3.30).

Subgrouping by PUFA dose and duration did not suggest important differences between subgroups (Analysis 3.31; Analysis 3.32). We did not plan to run meta-regressions for continuous outcomes. Subgrouping by primary or secondary prevention, baseline PUFA intake, replacement, age, sex, statin use and intervention type did not suggest important differences between subgroups (Analysis 3.33; Analysis 3.34; Analysis 3.35; Analysis 3.36; Analysis 3.37; Analysis 3.38; Analysis 3.39).

We did not downgrade the GRADE assessment of evidence. Higher PUFA intake leads to lower total cholesterol (high-quality evidence).

Lipids - serum fasting triglyceride

Higher PUFA intake probably leads to lower triglyceride levels (moderate-quality evidence).

Twenty trials incorporating data from 3905 participants (and 22 trial arms) provided data on serum triglycerides. Meta-analysis suggested that increasing PUFA intake reduced triglycerides, although data were heterogeneous (MD -0.12 mmol/L, 95% CI -0.20 to -0.04, $I^2 = 50\%$; Analysis 3.40). The funnel plot did not suggest small study bias, but we are aware of a further eight trials

that did not report triglycerides in a way that could be incorporated into meta-analysis (Ahn 2016; EPOCH 2011; NDHS Faribault 1968; NDHS Open 1st 1968; ORL 2013; Rossing 1996; WAHA - Ros 2016; WINS 2006).

Sensitivity analyses, including fixed-effect analysis, all suggested greater triglyceride reduction with higher PUFA intake, although some were not statistically significant (Analysis 3.41; Analysis 3.42).

Subgroup analyses did not suggest differential effects by dose, duration, baseline PUFA intake, replacement, statin use, intervention type, primary or secondary prevention, sex, or age (Analysis 3.43; Analysis 3.44; Analysis 3.45; Analysis 3.46; Analysis 3.47; Analysis 3.48; Analysis 3.49; Analysis 3.50).

We downgraded the GRADE evidence once for inconsistency. Higher PUFA intake probably leads to lower triglyceride levels (moderate-quality evidence).

Lipids - high density lipoprotein (HDL)

Higher PUFA intake probably has no important effects on HDL (moderate-quality evidence).

Eighteen trials incorporating data from 4674 participants (and 20 trial arms) provided data on HDL. Meta-analysis suggested that increasing PUFA intake had little or no effect on HDL, without heterogeneity (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, I^2 = 0%; Analysis 3.52). The funnel plot suggested that some trials with lower HDL in the higher PUFA arms may be missing, and adding any such trials into the meta-analysis would tend to lead to lower HDL with higher PUFA. We are aware of five trials that measured HDL but did not report the data in a way that could be incorporated into meta-analysis (EPOCH 2011; ORL 2013; Rossing 1996; WAHA - Ros 2016; WINS 2006).

Sensitivity analyses, including fixed-effect analysis, all confirmed lack of an important effect (Analysis 3.53; Analysis 3.54).

Subgrouping did not suggest differential effects of PUFA dose, duration, primary or secondary prevention, baseline PUFA intake, replacement, sex, age, statin use or intervention type (Analysis 3.55; Analysis 3.56; Analysis 3.57; Analysis 3.58; Analysis 3.69; Analysis 3.61; Analysis 3.62; Analysis 3.63).

We downgraded the GRADE assessment for publication bias. Higher PUFA intake probably has no important effects on HDL (moderate-quality evidence).

Lipids - low density lipoprotein (LDL)

Higher PUFA intake probably has no important effects on LDL (moderate-quality evidence).

Fifteen trials incorporating data from 3362 participants (and 17 trial arms) provided data on LDL. Meta-analysis suggested that increasing PUFA intake had little or no effect on LDL, without major heterogeneity (MD -0.01 mmol/L, 95% CI -0.09 to 0.06, I 2 = 44%; Analysis 3.64). The funnel plot suggested that some trials

with lower LDL associated with higher PUFA may be missing, adding such trials in would tend to suggest that increasing PUFA reduces LDL. We are aware of three trials that measured LDL but did not report it in a way that could be included in meta-analysis (Dullaart 1992; EPOCH 2011; ORL 2013).

Sensitivity analyses, including fixed-effect analysis, all confirmed this lack of effect (Analysis 3.65; Analysis 3.66).

Subgrouping did not suggest differential effects of PUFA dose, duration, primary or secondary prevention, baseline PUFA intake, replacement, sex, age, statin use or intervention type (Analysis 3.68; Analysis 3.69; Analysis 3.70; Analysis 3.71; Analysis 3.72; Analysis 3.73; Analysis 3.74; Analysis 3.75).

We downgraded the GRADE assessment for publication bias. Higher PUFA intake probably has no important effects on LDL (moderate-quality evidence).

Tertiary outcomes

We did not formally systematically review tertiary outcomes. Where the included trials reported these outcomes, we collated and analysed them.

Blood pressure, systolic and diastolic

Nine trials reported systolic blood pressure from 7356 participants, and eight trials reported diastolic blood pressure from 7327 participants. There was no suggestion of an effect of increased PUFA on systolic (MD -0.47 mmHg, 95% CI -2.20 to 1.26, $I^2 = 47\%$; Analysis 4.1) or diastolic blood pressure (MD 0.24 mmHg, 95% CI -0.55 to 1.02, $I^2 = 31\%$; Analysis 4.2). There were insufficient trials to assess the funnel plots, but we are aware of four trials that assessed blood pressure and did not report it fully (EPOCH 2011; MRC 1968; NDHS Open 1st 1968; Rossing 1996), though the data from MRC 1968 are displayed in the forest plot. We did not plan to carry out sensitivity analyses, subgroup analyses or metaregressions for these outcomes. Six of the trials in each analysis had low risk of bias from allocation concealment, and six were at low summary risk of bias. Lack of reporting of this commonly collected outcome may suggest publication bias, and the four trials with missing data would tend to confirm this.

Quality of life

One trial (Dodin 2005) assessed the effect of their flaxseed intervention on quality of life, using the MENQOL scale. MENQOL assesses the impact of four domains (vasomotor, psychosocial, physical and sexual) of menopausal symptoms over the previous month with scores ranging from 0 (no impact, high quality of life) to 32 (very poor quality of life in all domains). They found that over 12 months the MENQOL score fell slightly in both groups (intervention group -0.23, SD 0.62, N = 85, control group -0.14, SD 0.58, N = 94). This suggested little effect of the intervention on quality of life related to menopausal symptoms.

We found no further data on quality of life in the included trials, though dropouts may provide some information on how willing to continue the interventions participants were.

Economic costs

We did not find any data on economic costs in the included trials.

Serious adverse events

Adverse events reported in one or two trials each included the following, with no clear effects for any outcomes (Analysis 4.3).

- 1. Pulmonary embolism (RR 2.15, 95% CI 0.48 to 9.57, $I^2 = 0\%$, 2 trials, 2087 participants, 7 events)
- 2. Mutliple sclerosis worsened or acute attack (RR 1.11, 95% CI 0.95 to 1.30, $I^2 = 0\%$, 2 trials, 268 participants, 142 events)
- 3. Bleeding (RR 0.80, 95% CI 0.34 to 1.85, $I^2 = 0\%$, 2 trials, 748 participants, 21 events)
- 4. Gastrointestinal hospitalisation (RR 1.75, 95% CI 0.53 to 5.79, 1 trial, 200 participants, 11 events)
- 5. Retinopathy diagnosis (RR 1.02, 95% CI 0.56 to 1.86, 1 trial, 2424 participants, 42 events)

Effects of increased PUFA intake on dementia and neurocognitive outcomes (Jimoh 2017), type 2 diabetes and measures of glucose metabolism (Brown 2017), inflammatory bowel disease and inflammatory markers (Thorpe 2017), cancers (Hanson 2017b), depression and anxiety (Hanson 2017a) and functional outcomes (Abdelhamid 2017) are systematically reviewed elsewhere, so we have not reported results of effects seen in trials included in this review, as they are a potentially misleading subset. The systematic reviews on these health outcomes are not yet published, so we have provided references to their protocols so that the systematic reviews can be located.

Effects of increasing PUFA on pulmonary embolism and bleeding are unclear as the evidence is of very low quality.

Dropouts

Twenty-seven trials reported 1675 dropouts, suggesting that being in the higher or lower PUFA arm did not make much difference to the likelihood of dropping out (RR 0.99, 95% CI 0.87 to 1.13, $I^2 = 41\%$; Analysis 4.4). This may suggest that increasing PUFA is an acceptable intervention.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Higher PUFA compared to lower PUFA - dichotomous secondary outcomes for prevention of cardiovascular disease

Patient or population: people with or without existing cardiovascular disease, men and women

Setting: includes free-living participants and those living in institutions. Includes participants from all continents but most events and assessments occurred in trials carried out in Europe or North America.

Intervention: higher PUFA intake Comparison: lower PUFA intake

Eligible trials compared higher with lower total PUFA intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements had to aim to increase or decrease total PUFA intake, or a dietary component high in total PUFA intake such as vegetable oil, or, if no clear aim was stated (but implied, such as aiming to provide a 'heart health', 'reduced fat' or 'Mediterranean' diet) then the intervention had to achieve an increase or decrease of at least 10% of the baseline total PUFA level

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with lower PUFA	Risk with higher PUFA				
Cardiovascular mortal- ity Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)		RR 1.02 (0.82 to 1.26)	15,107 (16 RCTs)	⊕⊕⊜⊝ Low ^a	Increasing PUFA intake may have little or no
	36 per 1000	31 per 1000 (19 to 50)				effect on cardiovascular mortality (risk alters from 4.8% to 4.9% in the
	CVD at baseline (secondary prevention)					study population), low- quality evidence
	57 per 1000	64 per 1000 (52 to 77)				
Cardiovascular events Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)		RR 0.89 (0.79 to 1.01)	17,799 (21 RCTs)	⊕⊕⊕⊖ Moderate ^b	Increasing PUFA intake probably reduces risk of CVD events (from 14. 6% to 13.0% in the study population, NNT = 63), moderate-quality evidence

	54 per 1000	46 per 1000 (39 to 54)				
	CVD at baseline (secondary prevention)					
	233 per 1000	208 per 1000 (175 to 245)				
Coronary heart disease mortality Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)		RR 0.91 (0.78 to 1.06)	8810 (9 RCTs)	⊕⊕⊖⊖ Low ^c	Increasing PUFA intake may reduce risk of CHD
	52 per 1000	44 per 1000 (16 to 122)				death (from 6.6% to 6. 1% in the study popula- tion, NNT = 200), low-
	CVD at baseline (secondary prevention)					quality evidence
	68 per 1000	61 per 1000 (53 to 72)				
Atrial fibrillation and arrhythmias Follow-up: range 12 months to 60 months	No CVD at baseline (primary prevention)		RR 0.87 (0.72 to 1.06)	11692 (11 RCTs)	$\oplus\bigcirc\bigcirc\bigcirc$ Very low d	The effect of increasing PUFA intake on atrial
	26 per 1000	34 per 1000 (25 to 46)				fibrillation is unclear as the evidence is of very low quality
	CVD at baseline (secondary prevention)					
	119 per 1000	95 per 1000 (80 to 114)				
Adiposity - body weight, kg Follow-up: range 12 months to 60 months	Mean body weight was 81.0 kg	MD 0.76 higher (0.34 higher to 1.19 higher)	-	7100 (13 RCTs)	⊕⊕⊕⊖ Moderate ^e	Higher PUFA intake probably causes increased weight gain.

Adiposity - BMI, kg/m ² follow-up: range 12 months to 60 months	Mean BMI was 26.9 kg/ m ²	MD 0.17 higher (0.08 lower to 0.42 higher)	-	4798 (8 RCTs)	$\oplus \oplus \bigcirc \bigcirc$ Low f	Higher PUFA intake may increase BMI.
Serum total choles- terol (TC, mmol/L) Follow-up: range 12 months to 96 months	Mean serum TC was 5. 46 mmol/L	MD 0.12 lower (0.23 lower to 0.02 lower)	-	8072 (27 RCTs)	⊕⊕⊕⊕ High ^g	Higher PUFA intake leads to lower TC.
	Mean serum TG was 1. 57 mmol/L	MD 0.12 lower (0.2 lower to 0.04 lower)	-	3905 (20 RCTs)	⊕⊕⊕⊝ Moderate ^h	Higher PUFA intake probably reduces TG levels.
Serum high-den- sity lipoprotein (HDL, mmol/L) Follow-up: range 12 months to 60 months	Mean serum HDL 1.31 mmol/L	MD 0.01 lower (0.02 lower to 0.01 higher)	-	4674 (18 RCTs)	⊕⊕⊕⊝ Moderate ⁱ	Higher PUFA intake probably has little or no effect on HDL.
Serum low-density lipoprotein (LDL, mmol/L) Follow-up: range 12 months to 60 months	Mean serum LDL 2.86 mmol/L	MD 0.01 lower (0.09 lower to 0.06 higher)	-	3362 (15 RCTs)	⊕⊕⊕⊝ Moderate ^j	Higher PUFA intake probably has little or no effect on LDL.

^{*}The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

BMI: Body Mass Index; CI: confidence interval; CVD: cardiovascular disease; MD: mean difference; OR: odds ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^aCardiovascular mortality

- 1. **Risk of bias**: limiting trials to those at low summary risk of bias, low risk from allocation concealment, from attention bias, from compliance, by trial funding and trial size suggests small benefits and harms from increasing PUFA intake. Tends to confirm lack of important effect. Not downgraded.
- 2. Inconsistency: I² statistic less than 50%, not downgraded.
- 3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.
- 4. Imprecision: 95% confidence intervals range from important benefit to important harm. Downgraded twice.
- 5. **Publication bias**: some suggestion that one or two small trials may be missing. If added in they would tend to increase the RR. Not a large effect, not downgraded.

^bCardiovascular events

- 1. **Risk of bias**: sensitivity analyses suggested reduced risk of CVD events with more PUFA, lack of effect, and some harm. Downgraded once.
- 2. **Inconsistency**: I² statistic less than 50%, not downgraded.
- 3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.
- 4. **Imprecision**: over 17,000 participants randomised, of whom more than 2400 experienced CVD events. 95% confidence intervals excluded important harms. Not downgraded.
- 5. Publication bias: no suggestion of missing trials in the funnel plot. Not downgraded.

^cCoronary heart disease mortality (CHD)

- 1. Risk of bias: all sensitivity analyses concurred that increased PUFA reduced risk of CHD deaths. Not downgraded.
- 2. **Inconsistency**: I² statistic less than 50%, not downgraded.
- 3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.
- 4. **Imprecision**: over 8800 participants randomised and over 500 CHD deaths. However, the 95% confidence intervals didn't exclude important harm. Downgraded once.
- 5. **Publication bias**: some suggestion of publication bias. If present replacing missing trials would tend to raise the risk ratio towards 1.0 (no effect). Downgraded once.

^dAtrial fibrillation and arrhythmias

- 1. **Risk of bias**: no included trials were at low risk of compliance problems, all other sensitivity analyses suggested reduced risk of AF with increased PUFA. However there was no dose response, a suggestion of benefit in short trials, and harm in longer trials supported by meta-regression. Downgraded once.
- 2. **Inconsistency**: I² statistic greater than 50%. Downgraded once.
- 3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.
- 4. Imprecision: 95% confidence intervals exclude serious harm, but included the null. Downgraded once.
- 5. Publication bias: no suggestion of missing trials in the funnel plot. Not downgraded.

^eAdiposity - body weight

- 1. **Risk of bias**: sensitivity analyses assessing effects of different biases all suggested greater weight gain in those taking higher total PUFA. Not downgraded.
- 2. **Inconsistency**: I² statistic greater than 50% but partially explained by type of intervention and duration of intervention. Not downgraded.
- 3. Indirectness: weight was assessed in both men and women, but all trials were conducted in high-income countries. Not downgraded.

- 4. Imprecision: 95% confidence intervals only included increased weight with increased PUFA intake. Not downgraded.
- 5. **Publication bias**: the funnel plot suggests that some trials with less weight gain in the higher PUFA arm may be missing. Two trials with weight data could not be included in meta-analysis, but they also suggested greater weight gain in the higher PUFA arm. Other missing trials, if due to publication bias, are likely to have not been published because they suggested increased weight in the higher PUFA arm, so are likely to support the main analysis. Downgraded once.

^f Adiposity - Body Mass Index (BMI)

- 1. **Risk of bias**: sensitivity analyses assessing effects of different biases all suggested greater weight gain in those taking higher total PUFA. Not downgraded.
- 2. Inconsistency: 12 statistic greater than 50%, and not explained by subgrouping. Downgraded once.
- 3. Indirectness: weight was assessed in both men and women, but all trials were conducted in high-income countries. Not downgraded.
- 4. Imprecision: 95% confidence intervals did not include important benefits, but did include the null. Downgraded once.
- 5. Publication bias: no suggestion of missing data. Not downgraded.

§Serum total cholesterol (TC)

- 1. Risk of bias: sensitivity analyses all suggested greater lipid reduction with higher PUFA intake. Not downgraded.
- 2. **Inconsistency**: I² statistic greater than 50%, and while no single factor explains this there were greater TC reductions with low statin use, higher PUFA dose, lower baseline PUFA, and replacement of saturated fats and monounsaturated fats. Not downgraded.
- 3. **Indirectness**: data provided by men and women, and comes from high-income and low- to middle-income countries. Not downgraded.
- 4. **Imprecision**: data came from thousands of participants and 95% confidence intervals did not include harm. Not downgraded.
- 5. **Publication bias**: funnel plot not interpretable, known missing data are consistent with data used in meta-analysis. Not downgraded.

^hSerum triglycerides (TG)

- 1. Risk of bias: sensitivity analyses all suggested greater lipid reduction with higher PUFA intake. Not downgraded.
- 2. **Inconsistency**: 1² statistic = 50%, without any clear explanation from subgrouping. Downgraded once.
- 3. **Indirectness**: data provided by men and women, and comes from high-income and industrialising countries. Not downgraded.
- 4. **Imprecision**: data came from thousands of participants and 95% confidence intervals did not include harm. Not downgraded.
- 5. Publication bias: no suggestion of missing data. Not downgraded.

i Serum HDL

- 1. Risk of bias: consistent lack of effect of PUFA in all sensitivity analyses. Not downgraded.
- 2. **Inconsistency**: I² statistic less than 50%. Not downgraded.
- 3. **Indirectness**: data provided by men and women, and comes from high-income and industrialising countries. Not downgraded.
- 4. **Imprecision**: data came from thousands of participants and confidence interval excludes important effects. Not downgraded.
- 5. **Publication bias**: some trials with lower HDL appear to be missing. Downgraded once.

^jSerum LDL

- 1. Risk of bias: consistent lack of effect of PUFA in all sensitivity analyses. Not downgraded.
- 2. Inconsistency: I² statistic less than 50%. Not downgraded.
- 3. Indirectness: data provided by men and women, and comes from high-income and industrialising countries. Not downgraded.
- 4. **Imprecision**: data came from thousands of participants and confidence interval excludes important effects. Not downgraded.
- 5. **Publication bias**: some trials with lower LDL appear to be missing. Downgraded once.

DISCUSSION

Summary of main results

This Cochrane Review included 49 RCTs randomising 24,272 participants, for one to eight years. We identified 22 potential ongoing trials. Total PUFA dose (the difference in total PUFA between intervention and control arms) was 0.6% E to less than 1% E for 13 trials, 1% E to less than 2% E in 17 trials, 2% E to less than 5% E in eight trials, and 5% E or more from total PUFA in 11 trials. We assessed 11 of the 49 included trials as being at low summary risk of bias.

Increasing PUFA intake probably has little or no effect on all-cause mortality (risk changes from 7.8% to 7.6%, RR 0.98, 95% CI 0.89 to 1.07, $I^2 = 0\%$, 1443 deaths, 24 trials, moderate-quality evidence, downgraded for imprecision). Increasing PUFA probably reduces the risk of coronary heart disease events (from 14.2% to 12.3%, RR 0.87, 95% CI 0.72 to 1.06, $I^2 = 45\%$, 1351 people with coronary heart disease events, 15 trials, moderate quality evidence, downgraded for imprecision and risk of bias combined) and stroke (from 1.2% to 1.1%, RR 0.91, 95% CI 0.58 to 1.44, I $I^2 = 24\%$, 166 strokes, 11 trials, however the confindence intervals included important harm, low-quality evidence downgraded once for imprecision and once for risk of bias and imprecision combined). Effects on MACCEs (RR 0.84, 95% CI 0.59 to 1.20, I $I^2 = 79\%$, 817 events, 2 trials) are unclear as evidence is of very low quality (downgraded for risk of bias, imprecision and inconsistency).

For secondary outcomes we found that increasing PUFA intake probably reduces risk of cardiovascular disease events (from 14.6% to 13.0%, RR 0.89, 95% CI 0.79 to 1.01, $I^2 = 30\%$, 2442 events, 21 trials, moderate-quality evidence). Increasing PUFA intake may slightly reduce risk of coronary heart disease death from 6.6% to 6.1% (RR 0.91, 95% CI 0.78 to 1.06, $I^2 = 0\%$, 556 coronary heart disease deaths, 9 trials) and myocardial infarction (RR 0.88, 95% CI 0.78 to 0.99, I² = 0%, 880 myocardial infarctions, 15 trials) but may increase the risk of peripheral arterial disease (RR 1.20, 95% CI 0.81 to 1.77, $I^2 = 0\%$, 97 events, 4 trials) and have little or no effect on cardiovascular mortality (4.8% to 4.9%, RR 1.02, 95% CI 0.82 to 1.26, $I^2 = 31\%$, 729 cardiovascular disease deaths, 16 trials), all low-quality evidence. The effect of increasing PUFA on sudden cardiac death, angina, atrial fibrillation, heart failure and revascularisation is unclear as the evidence is of very low quality.

High-quality evidence suggests that increasing PUFA intake slightly reduces total serum cholesterol over at least one year (MD -0.12 mmol/L, 95% CI -0.23 to -0.02, I^2 = 79%, 8072 participants, 26 trials). Increasing PUFA intake probably causes some weight gain (MD 0.76 kg, 95% CI 0.34 to 1.19, I^2 = 59%, 7100 participants, 12 trials), decreases triglycerides (MD -0.12 mmol/L, 95% CI -0.20 to -0.04, I^2 = 50%, 3905 participants, 20 trials) and has little effect on HDL (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, I^2 = 0%, 4674 participants, 18 trials) or LDL (MD -0.01

mmol/L, 95% CI -0.09 to 0.06, I^2 = 44%, 3362 participants, 15 trials) (all moderate-quality evidence).

There was limited information on blood pressure, quality of life, economic outcomes or adverse health effects. Effects of increasing PUFA on pulmonary embolism and bleeding are unclear as the evidence is of very low quality. Effects of PUFA intake on other serious adverse health effects (cancers, inflammatory bowel disease, depression or anxiety, neurocognitive outcomes, functional outcomes and diabetes) are systematically reviewed and reported elsewhere.

We looked for dose and duration effects using subgrouping and meta-regression, finding none except a duration effect in atrial fibrillation, with protective effects in shorter trials (up to two years), little or no effect in trials of two to less than four years, and harm in longer trials (Analysis 2.43). We found no evidence of no linear dose effects, though assessment of PUFA doses actually delivered by trials were difficult to ascertain, often due to missing control information. Baseline PUFA intake (or PUFA intake in the control group as a proxy) were poorly reported, reducing our ability to see subgroup differences - there was a suggestion of greater benefit of PUFA with lower baseline PUFA intake for cardiovascular disease mortality, but not for other cardiovascular outcomes.

There were no clear patterns of differential effects across outcomes by primary or secondary prevention, replacement, sex, age, statin use or intervention type. Subgrouping did not suggest differences between effects in primary or secondary prevention, except for atrial fibrillation, where increasing PUFA in primary prevention was harmful and increasing PUFA in secondary prevention was beneficial (Analysis 2.44). There were no differential effects by replacement, sex or statin use. For cardiovascular disease mortality there was a suggestion of harm from increasing PUFA intake in younger adults, smaller levels of harm in middle-aged adults and benefit in those aged at least 65 years (Analysis 2.10). This pattern was repeated for cardiovascular disease events, except that some benefit was seen in the middle-aged group (Analysis 2.22), although this pattern was not seen for other outcomes. Dietary advice appeared to lead to greater increases in body weight and BMI (Analysis 3.12; Analysis 3.24), while dietary advice and supplements to increase PUFA appeared to reduce triglyceride to a greater extent than supplemental foods or diet provided (Analysis 3.51).

Overall completeness and applicability of evidence

Included trials randomised 24,272 participants over periods of at least a year. Participants were men and women aged from their 20s into their 80s but most trials recruited participants with a mean age of 50 to 65 years. Most coronary heart disease events occurred in these 'middle-aged' trials, but most deaths occurred in trials of older adults. Twenty-two trials included 70% or more men, and many of these were exclusively in men, six included 70% or more

women, and sixteen included a balanced proportion of men and women. Despite this, most coronary heart disease events (1289 of 1351) and deaths (1134 of 1443) occurred in trials mainly of men, so while women are included it is not clear whether any effects are generalisable to them. Similarly, while younger adults are included, most events occurred in older adults, which partly explains the lack of appearance of some trials of younger adults in many of the analyses on health events. We included these trials as they reported data on lipids or adiposity, or both, and sometimes one or two health events.

Two included trials were from countries with developing economies (Mendis 2001 from Sri Lanka and Vijayakumar 2014 from India) but while both provided lipid data, the only events were two deaths in Vijayakumar 2014. This means that the bulk of the information in this review is from countries with developed economies. Some trials were from areas with non-western dietary practices, including South Korea (Ahn 2016), Japan (DIPP-Tokudome 2015; Doi 2014; Mita 2007; ORL 2013), Sri Lanka (Mendis 2001), and India (Vijayakumar 2014), however often the dietary intakes of these populations at baseline and during the trial were not well described.

Our data spring from trials conducted from the 1960s (MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Veterans Admin 1969) to the present, and during this sixty year period cardiovascular disease incidence has altered. For example, in 2010 one in four deaths worldwide was from ischaemic heart disease or stroke, up from one in five in 1990 (Lozano 2012). But this worldwide increase hides more complex trends, with different rates and trends in different parts of the world. Death rates from CHD in men aged 35 to 74 were 839/100,000 in Ukraine in 2000, but ~200/100,000 in the USA and UK, and only 54/100,000 in Japan. Rates in women were lower but followed the same trends by country (WHO 2004). In the UK as in most high-income countries age-standardised death rates from coronary heart disease in adults of all ages fell by 72% between 1979 and 2013, and stroke mortality fell by 71% over the same period (Bhatnagar 2016). Globally age-adjusted annual incidence of stroke in men and women of all ages has increased slightly from 1990 to 2010, but this masks falls in high-income countries and rises in low and middle-income countries (Feigin 2014; Carandang 2006). While we assess effects using risk ratios in this review so that we can see relative effects regardless of baseline incidence, baseline incidence affects absolute effects including numbers needed to treat. Our results suggest that we need to increase total PUFA intake in -53 people to prevent one person experiencing a CHD event, in ~63 people to prevent a CVD event, and even more for CHD death and stroke. But in populations at greater risk NNTs will be lower (fewer people needing to increase their PUFA to prevent one person experiencing an event), and in lower risk populations NNTs will be higher. The greatest import of dietary increases in total PUFA intake is likely to be in low- and middleincome countries where rates of CVD are higher (and rising).

Results relate to both primary and secondary prevention of cardiovascular disease. However, as would be expected, most events occurred in those with existing cardiovascular disease. For example, 1130 of 1443 deaths (78%) were in participants with cardiovascular disease at baseline (Analysis 1.6). Effects in the secondary prevention group (risk barely altering from 11.7% in the lower PUFA arm to 11.5% (95% CI 10.1 to 13.1%) in the higher PUFA arm) were similar to those without cardiovascular disease at baseline (primary prevention, risk barely altering from 3.4% in the lower PUFA arm to 3.3% (95% CI 2.7 to 4.1%) in the higher PUFA arm). For cardiovascular disease events 2013 of 2435 people (83%) experiencing cardiovascular disease events had existing cardiovascular disease at baseline (Analysis 2.18). Risk of a cardiovascular disease event fell by 2.5% from 23.3% to 20.8% (95% CI 17.5% to 24.5%) in secondary prevention, and fell by 0.9% from 5.8% to 4.9% (95% CI 4.2% to 5.9%) in primary prevention when increasing PUFA intake.

We are aware of missing trials. We were unable to access data for AFORRD; NCT00309439; NCT00410020; Chandrakala 2010 or ACTRN12610000594022, which all appeared likely to be eligible. They were all registered before the end of 2010 or had planned finish dates up to the end of 2015, hence appear to be completed but unpublished (see Characteristics of ongoing studies). We are also aware of some missing data within included trials for example there were deaths in Bates 1977 but they were reported combined with dropouts and the trial author no longer has the data, and two deaths in Simon 1997 not reported by intervention arm. Houtsmuller 1979 reported coronary heart disease events and mortality, but not all-cause deaths or cardiovascular disease events. Sixteen trials (Ahn 2016; Black 1994; Dullaart 1992; EPOCH 2011; HERO-Tapsell 2009; MARINA - Sanders 2011; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; ORL 2013; Rossing 1996; Simon 1997; Veterans Admin 1969; Vijayakumar 2014; WAHA - Ros 2016; WINS 2006) reported at least one continuous outcome without variance data or without change data and with baseline data too different to allow us to use end data (so we missed at least six sets of data on total cholesterol, eight on triglyceride, seven on body weight and four sets on blood pressure). On the other hand, we were provided the full dataset on events for DART fat 1989, so were able to include data for almost all of our outcomes, data for Sydney Diet-Heart 1978 were well reported in recent re-analyses and the trial authors kindly augmented these data, and outcome data in Veterans Admin 1969 were very well reported, so data are probably almost complete for these large trials. Authors of many other trials provided some additional data on outcomes and/or confirmed that no participants experienced specific outcomes.

We identified 22 potential ongoing trials (Characteristics of ongoing studies), but these trials are very difficult to assess for inclusion in terms of total PUFA dose, until further details are published. We will formally assess these trials for inclusion when we update this review. Two of these trials specifically include women,

who are underrepresented in trials already included in this review (NCT01784042; NCT02295059). Other ongoing trials appear generally to be in both men and women, which will increase the proportion of data provided by women. Two trials appear to be planned for developing economies (India Chandrakala 2010 and China n-3 on plasma lipid), but the majority appear to be carried out in Europe, North America and Australia. It is not possible to assess whether any of these trials will document trans fat intake or status, or indeed intake or status of other key fats and nutrients. There is no suggestion that any of these trials are targeting participants with low baseline total PUFA intakes. Overall, they may begin to address information about women more thoroughly, but not deficiencies in the database of information on participants from lower-income countries, and they are not clearly of higher quality when it comes to assessment of dietary intakes and nutritional status before and during the trials.

We all consume PUFA already (it is essential in our diets). It would be useful to understand whether increasing PUFA in people who eat very little has the same effect as increasing PUFA in people already consuming large amounts. Unfortunately few trials assessed overall dietary intake of participants at baseline or through the trial. Only 16 of the 49 included trials provide information on baseline or control-arm PUFA intake (we used control-arm PUFA intake in lieu of baseline PUFA intake where no baseline intake was given and the control arm were on 'usual intake'). Of these 16 trials, participants in seven consumed less than 6% E from PUFA and nine 6% E and above. Despite these limited data there is a pattern across the review that effects in participants with less than 6% E PUFA intake at baseline are positive, but effects in those with higher baseline PUFA intake are negative or neutral - though we do not see statistically significant differences between subgroups and data are very limited. The pattern is evident for coronary heart disease events (Analysis 1.19), stroke (Analysis 1.31), MACCEs (Analysis 1.45), cardiovascular disease mortality (Analysis 2.7), and cardiovascular disease events (Analysis 2.19), but not in all-cause mortality where no effects are seen in any group (Analysis 1.7) or coronary heart disease mortality (Analysis 2.31), and we lack data for atrial fibrillation. This relationship needs to be checked in future trials, but suggests that increasing total PUFA intake to at least 6% E may be appropriate.

Other subgrouping and meta-regression effects that would tend to support true effects of increasing total PUFA on some cardiovascular outcomes include seeing greater effects with higher PUFA doses or with longer duration (for dichotomous outcomes). We consistently do not see dose or duration effects within the review, and this weakens our findings of health effects arising from increasing PUFA.

Total PUFA is the sum of omega-3, omega-6 and some omega-9 fats, which may have their own specific effects on our outcomes. We have assessed specific effects of omega-3 (Abdelhamid 2018) and omega-6 (Hooper 2018) in separate reviews, but this review aims to assess whether there is a group effect of PUFAs. It would

be useful to assess effects of omega-3/omega-6 ratio in this review - but these data are not available. Similarly data on trans fats would be useful, as it is possible that some trials increased trans fats when providing PUFA (through use of partially hydrogenated fats). There is evidence that trans fats may be harmful (de Souza 2015), and so may confound our understanding of the PUFA trials. Unfortunately almost no information on trans fat intake was found, so we could not assess this issue.

Despite systematic review evidence that omega-3 fats do not influence cardiovascular disease risk (Abdelhamid 2018) there is a theory that the ratio of omega-3 to omega-6 fats is important for cardiovascular health and body weight (Simopoulos 2016). We planned to subgroup by change in the omega-3/omega-6 fat ratio, assessing whether the intervention primarily increased omega-3 fats (putting up the ratio) or omega-6 fats (lowering the ratio). However, only three trials (DIPP-Tokudome 2015; PREDIMED 2013; WAHA - Ros 2016) reported both omega-3 and omega-6 intakes (understanding supplemental intakes only would not be adequate). This means that we cannot use this review to assess health effects of altering the omega-3/omega-6 ratio.

There were no clear dose or duration effects in the review. While we would expect that replacing saturated fat, MUFA or carbohydrate with PUFA would give different health effects, we do see greatest reduction in total cholesterol with replacement of saturated fat (Analysis 3.35), and greatest reduction of triglyceride with replacement of MUFA (Analysis 3.47). However, there are no statistically significant differences between subgroups for these outcomes or any other health outcomes. There are no clear replacement effects. It is also surprising to see increased PUFA intake reducing total cholesterol and triglyceride (Analysis 3.28; Analysis 3.40), with no change in LDL (Analysis 3.64). The Friedewald equation (Friedewald 1972) states that 'total cholesterol = LDL + HDL + triglyceride/2.19' (all components in mmol/L), so for the changes of total cholesterol and triglyceride we see, we would expect similar falls in LDL, but this is not seen. Reasons for this are not clear, but it is possible that changes in very low density lipoprotein (VLDL) added to triglyceride reductions and very small changes in HDL and LDL could add up to the overall total cholesterol reduction. Overall, included data are applicable, but not entirely complete. While further trials of increasing PUFA intake in women and in developing economies are needed, they should include participants with low PUFA intakes at baseline, as well as those with higher intakes. Dietary advice needs to ensure that trans fat intake is kept low as PUFA increases, and intakes of all fat fractions, including trans fat intakes should be assessed and checked using reliable biomarkers.

Quality of the evidence

GRADE assessment includes consideration of risk of bias, inconsistency, indirectness, publication bias and imprecision (Summary of findings for the main comparison and Summary of findings 2).

We assessed risk of bias by assessing whether effect sizes and directions altered when limited to trials at low risk of bias from allocation concealment, from attention bias, from compliance, trials at low summary risk of bias, with trials registry registration (or pre-2010), without industry funding, and that randomised at least 100 or 250 participants. Sensitivity analyses generally supported the primary analysis for all-cause mortality, coronary heart disease mortality, cardiovascular disease mortality, weight and lipid outcomes (Analysis 1.2; Analysis 2.2; Analysis 2.14; Analysis 2.26; Analysis 3.2; Analysis 3.14; Analysis 3.29; Analysis 3.41; Analysis 3.53; Analysis 3.65), so we did not downgrade these for risk of bias. Either sensitivity analyses contradicted the primary analyses (for coronary heart disease events and stroke; Analysis 1.14; Analysis 1.26) or there were no trials at low summary risk of bias, or low risk of compliance problems (MACCEs and atrial fibrillation; Analysis 1.40; Analysis 2.40), so we downgraded these outcomes for risk

We judged imprecision by whether the 95% CI included the null, and whether it included important benefits and harms. Where both important benefits and harms were included within the confidence interval we downgraded twice, where it only included the null we downgraded once unless there was a very small overlap. We downgraded the evidence on all primary and some secondary outcomes for imprecision, suggesting that included trials may still be underpowered to determine effectiveness on these outcomes. There was no evidence of under-powering for lipid outcomes.

We judged inconsistency using the I² statistic for each primary and secondary outcome. We considered an I² statistic greater than 50% to be a problem and led to us downgrading for inconsistency unless we found an element that explained that inconsistency (through subgrouping or meta-regression). We downgraded the primary outcome, MACCEs for inconsistency, and also secondary outcomes, atrial fibrillation, BMI and triglyceride.

We judged indirectness according to whether data on an outcome related to both women and men, those with and without cardio-vascular disease at baseline, and whether low- and middle-income, and high-income countries were represented. While indirectness is important, we suspect that the mechanisms of action of PUFA are similar in all these populations so we did not downgrade for indirectness.

We judged publication bias according to whether there was any suggestion of publication or small study bias in the funnel plot, or where we knew that data were missing that differed from the summary assessment. We downgraded the secondary outcomes, coronary heart disease mortality, body weight, HDL and LDL for publication bias.

Trial funding can be an important indicator of study bias but is not included in 'Risk of bias' assessment. Sixteen trials reported funding sources, which appeared to be purely from national or charitable agencies, seven trials appeared to be directly funded by industrial sources, two funded by bodies set up to promote specific foods, 16 by some governmental or charity sources with

additional funding or support from commercial sources, two trials included authors on industry honoraria, and five trials did not report funding.

Trial pre-registration or early publication of a trial protocol is helpful in understanding potential biases in data presentation (including outcome selection bias). We ran sensitivity analyses assessing whether trials that were pre-registered or had a published protocol suggested different effects than trials without such documentation. We found trials registry entries for most included trials published after 2010. Making datasets of all outcomes available via trials registers would also help systematic reviewers to gather all appropriate data, and minimise publication bias.

Applying the GRADE criteria suggests that we have high-quality evidence on effects of PUFA on serum total cholesterol (not downgraded), moderate-quality evidence on all-cause mortality, coronary heart disease events, cardiovascular disease events, body weight, triglyceride, HDL and LDL (each downgraded once), and low-quality evidence for stroke, cardiovascular disease mortality, coronary heart disease mortality and BMI (each downgraded twice). All other evidence was of very low quality. Reasons for grading, and statements of findings based on these levels of evidence are found in Summary of findings for the main comparison and Summary of findings 2.

Potential biases in the review process

We conducted a large number of sensitivity analyses and subgroup analyses for each primary outcome, as well as some secondary outcomes (key outcomes). The danger in these is that subgroups may be spuriously statistically significant, but we used them to check the stability of our primary analyses, as well as to try to explain heterogeneity, assessing for dose effects, duration effects and differential effects by what PUFA replaces in the diet. We have tried not to over-interpret any of these analyses.

We only considered trials with interventions or follow-up periods of 12 months or more, making the review relevant for public health interventions. We considered including shorter trials, but were concerned that if we found no effect then this might be due to including trials too short to reflect health effects of increasing or decreasing PUFA intake. The decision on duration depended on assumed mechanism of action of PUFA. If we assumed a cholesterol-led atherosclerotic mechanism then we could justify deciding only to include trials of at least two years' duration. However another mechanism discussed for omega-3 and omega-6 fats includes inflammation - likely to work more quickly than atherosclerosis, so allowing six months for equilibration of body tissues with the new dietary intake, and a further six months to allow for reflection of this new status in health outcomes, appears most appropriate to us. We ran subgroup analyses to assess whether trial duration made an important difference to our primary outcomes. We did not find any suggestion of greater effects in longer trials (those of at least four years) compared to shorter trials (one to less than

two years, or two to less than four years) for all-cause mortality (Analysis 1.5), coronary heart disease events (Analysis 1.17), or stroke (Analysis 1.29). Only two trials provided data on MACCEs, but these two trials did suggest a protective effect in the longer trial (Analysis 1.43). Meta-regression did not suggest duration effects for any primary outcome. Similarly there were no duration effects in subgrouping or meta-regression for cardiovascular disease mortality (Analysis 2.5), cardiovascular disease events (Analysis 2.17), or coronary heart disease mortality (Analysis 2.29), though visual inspection tended to suggest greater protection in the shortest trials, despite them reporting few events. There was a suggestion of a duration effect for atrial fibrillation, but the suggestion was for greater effect in shorter trials, and no effect in longer trials (Analysis 2.43). Conversely participants taking more PUFA gained more weight and their BMI rose more in longer trials (Analysis 3.5; Analysis 3.17).

Our inclusion criteria could potentially cause some bias. Few trials directly aimed to assess effects of increasing PUFA with usual or lower PUFA intake, so included trials are a combination of trials that aimed to increase PUFA, trials that aimed to increase omega-3 or omega-6 fats and resulted in an increase of at least 10% of baseline PUFA intake, and trials that aimed to reduce total fat intake and resulted in a decrease of at least 10% of baseline PUFA intake (while not aiming to alter dietary components other than fat or replacements for the change in PUFA). This allowed assessment of effects of altering PUFA intake, but we had to exclude trials that may have been relevant but did not report aims for or effects on total PUFA, so we may be missing other trials that would be relevant to this review. It is also possible that we included trials that aimed to increase or decrease total PUFA but did not achieve the planned changes in PUFA intake. To help guard against this we also conducted sensitivity analyses around compliance, removing trials where we did not have biomarker confirmation of a difference in PUFA status between trial arms.

Even though we excluded clearly multifactorial trials, when we alter one dietary component, other components inevitably alter too. For example, when PUFA intake is increased we need to reduce energy intake elsewhere, so saturated fat or carbohydrate intake may fall to compensate. The danger is that we may see a health effect from increasing PUFA that is actually due to a reduction in saturated fat. However, in this review some trials that increased PUFA reduced saturated fat, and in other trials PUFA and saturated fat were both reduced in the intervention arm. Regardless of which arm the trial considered to be the intervention arm we compared the arm with higher PUFA against the arm with lower PUFA to look for consistent effects of higher PUFA intake. Because saturated fat (and other dietary components) sometimes moved with PUFA and sometimes moved in the opposite direction the only consistent difference between arms was in PUFA intake. This means that health effects noted are unlikely to be spurious effects of other dietary components. Combining higher versus lower PUFA intake across different types of trials may balance out effects of other dietary (fat and non-fat) components while providing power to assess health effects of changing PUFA.

Agreements and disagreements with other studies or reviews

We recently published a Cochrane Review of long-term RCTs that assessed effects of reducing saturated fats, replacing them with a variety of other energy sources (Hooper 2015a). This review found no effect of reducing saturated fats on all-cause mortality or cardiovascular disease mortality, but the evidence suggested that reducing saturated fats reduced the risk of cardiovascular disease events (RR 0.83, 95% CI 0.72 to 0.96, $I^2 = 65\%$, including 4377 events in over 53,000 randomised participants). Subgrouping, assessing whether the saturated fats were being replaced by PUFA, MUFA, carbohydrate and/or protein found that there were no statistically significant effects in these subgroups except where saturated fat was being replaced by PUFA (RR 0.73, 95% CI 0.58 to 0.92, I^2 = 69%, 884 events in over 3000 participants). Hooper 2015a confirmed results expected from the Friedewald equation (Friedewald 1972). The trials included in the saturated fat review and this one are distinct due to rather different inclusion criteria (for example, the saturated fat review only included trials of at least two years duration, and included trials with dietary interventions decreasing saturated fat plus altering other dietary variables). The implications of the reviews are similar - Hooper 2015a suggests that reducing saturated fat and replacement by polyunsaturated fats reduces the risk of cardiovascular disease events, while this review also suggests that increasing PUFA may reduce the risk of cardiovascular disease events, as well as coronary heart disease mortality (as well as reducing total cholesterol and triglyceride). However, this current review also suggests that increasing PUFA intake also leads to slight weight gain.

Two previous systematic reviews of RCTs assessed effects of PUFA replacing saturated fat: Ramsden 2010 and Mozaffarian 2010. Ramsden 2010 included seven trials that compared increasing mixed omega-3 and omega-6 PUFA or omega-6 alone and replacing dietary saturated fat with usual dietary intake. Their data suggested no effect on all-cause mortality (RR 0.99, 95% CI 0.89 to 1.11), but likely reductions in coronary heart disease mortality (RR 0.91, 95% CI 0.74 to 1.10), and myocardial infarction and cardiac death combined (RR 0.85, 95% CI 0.73 to 0.99). These are similar results to this review (no effect on all-cause mortality, reductions in coronary heart disease mortality and myocardial infarction). Ramsden 2010 included fewer trials than this review, four trials that we included (MRC 1968; Rose 1965; Sydney Diet-Heart 1978; Veterans Admin 1969), and three we excluded. We excluded two for being multifactorial (Oslo Diet-Heart 1966; STARS 1992) and one for having inconsistent enrolment so that many participants were included for less than 12 months continuously (Minnesota Coronary 1989). The other systematic review, Mozaffarian 2010, also included seven trials replacing saturated fat with PUFA, three that we included (DART fat 1989; MRC 1968; Veterans Admin 1969), and four that we excluded. One we excluded due to lack of randomisation (Finnish Mental Hosp 1972), one for inconsistent enrolment (Minnesota Coronary 1989), and two because the intervention was multifactorial (Oslo Diet-Heart 1966; STARS 1992). Mozaffarian 2010 found that increasing PUFA by replacing saturated fat reduced coronary heart disease events by 19% (RR 0.81, 95% CI 0.70 to 0.95), unlike this review, where we found that the evidence was of very low quality, so could not assess effects on this outcome.

Recent observational data of more than 30,000 adults aged over 30 years from the National Health and Nutrition Examination Survey (NHANES) was not entirely consistent with our results. They suggested that the tertile of adults with highest PUFA intake were at lowest risk of all-cause mortality (HR 0.94, 95% CI 0.90 to 0.98 compared to the tertile with lowest intake) and cardiovascular disease mortality (HR 0.93, 95% CI 0.89 to 0.97), when adjusted for ethnicity, BMI, alcohol intake, smoking, education, physical activity, fibre intake and blood pressure (Ricci 2018).

The suggestion of weight gain with increased PUFA intake reflects data from other systematic reviews that reducing dietary fat (including PUFAs) appears to result in lower weight in adults. As weight gain may increase cardiovascular risk, this may work against more positive lowering of total cholesterol and triglycerides when assessing overall effects of increasing PUFA on cardiovascular disease (Hooper 2015b).

We interpreted the total cholesterol and weight results using QRisk 2-2017 (QRISK 2-2017). In a Pakistani non-smoking male aged 64 years without existing cardiovascular disease or diabetes, height 173 cm, weighing 81 kg with systolic blood pressure of 145 mmHg and total cholesterol 5.46 mmol/L, HDL 1.31 (total cholesterol/ HDL 4.17) at baseline (typical values for the trials in this review) their 10-year QRISK 2-2017 score would be 23.5%. A reduction of total cholesterol by 0.12 mmol/L, HDL by 0.01 mmol/L and weight rise of 0.76 kg reduces the QRISK 2-2017 score to 23.2%. QRISK 2-2017 suggests that in 1000 people with the same risk factors, 235 are likely to have a heart attack or stroke within the next 10 years at baseline, falling to 232 having a heart attack or stroke following increased PUFA intake. Three people of the 1000 would be prevented from experiencing a heart attack or stroke by the increased PUFA. This is a smaller effect than the estimated reduction from 58 per 1000 to 49 (95% CI 42 to 59) per 1000 predicted for primary prevention of cardiovascular disease events within this review (Summary of findings 2).

AUTHORS' CONCLUSIONS

Implications for practice

Increasing polyunsaturated fatty acid (PUFA) intake probably makes little or no difference (neither benefit nor harm) to all-

cause mortality and probably slightly reduces the risk of coronary heart disease events and cardiovascular disease events (all moderate-quality evidence). Increased PUFA intake may slightly reduce risk of coronary heart disease mortality and stroke (although for stroke the confidence intervals include important harm), but may have little or no effect on cardiovascular disease mortality (all low-quality evidence). Increasing PUFA does reduce total cholesterol, probably reduces triglyceride, probably has little or no effect on high-density lipoprotein (HDL) or low-density lipoprotein (LDL) and probably increases body weight.

This suggests that increasing PUFA intake may have beneficial effects on risk of cardiovascular disease events, coronary heart disease mortality, coronary heart disease events and stroke. The mechanism may be via reduction of total cholesterol and triglyceride. However increasing PUFA will probably lead to slight body weight increase.

Implications for research

Further trials assessing cardiovascular effects of increasing PUFA intake in women and people living in developing economies are needed. Given the low power for assessing effects by baseline PUFA, more research in populations with a low baseline intake of less than 6% E is needed to understand whether there is greater benefit from increasing PUFA intake in these groups. Further trials should include participants with low PUFA intakes at baseline, as well as those with higher intakes. Dietary advice needs to ensure that trans fat intake is kept low as PUFA increases. Intake and status of all fat fractions, including trans fat, should be assessed and checked using reliable biomarkers.

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(¹Norwich Medical School, University of East Anglia, ²Warwick Medical School, University of Warwick, ³School of Health Sciences, University of East Anglia, ⁴Cochrane Heart, University College London, ⁵Durham University, ⁶Clinical Nutrition Department, Faculty of Applied Medical Sciences, King Abdulaziz University, KSA, ⁷School of Dentistry, University of Manchester).

REFERENCES

References to studies included in this review

Ahn 2016 {published data only (unpublished sought but not used)}

Ahn J, Park SK, Park TS, Kim JH, Yun E, Kim SP, et al. Effect of n-3 polyunsaturated fatty acids on regression of coronary atherosclerosis in statin treated patients undergoing percutaneous coronary intervention. *Korean Circulation Journal* 2016;**46**(4):481–9. PUBMED: 27482256]

AlphaOmega - ALA {published and unpublished data}

Brouwer IA, Geleijnse JM, Klaasen VM, Smit LA, Giltay EJ, De Goede J, et al. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the Alpha Omega Trial. *PloS One* 2013;**8**(12): e81519.

Eussen SR, Geleijnse JM, Giltay EJ, Rompelberg CJ, Klungel OH, Kromhout D. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. *European Heart Journal* 2012;**33**(13):1582–8.

Geleijnse J, Giltay E, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's & Dementia 2011;1:S512.

Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. *Alzheimer's & Dementia* 2012;8(4):278–87. Geleijnse JM, Giltay EJ, Schouten EG, De Goede J, Oude Griep LM, Teitsma-Jansen AM, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: design and baseline characteristics of the Alpha Omega Trial. *American*

Heart Journal 2010;**159**(4):539–46. DOI: 10/1016/j.ahj.2009.12.033

Giltay EJ, Geleijnse JM, Heijboer AC, De Goede J, Oude Griep LM, Blankenstein MA, et al. No effects of n-3 fatty acid supplementation on serum total testosterone levels in older men: the Alpha Omega Trial. *International Journal of Andrology* 2012;35(5):680–7.

Giltay EJ, Geleijnse JM, Kromhout D. Effects of n-3 fatty acids on depressive symptoms and dispositional optimism after myocardial infarction. *American Journal of Clinical Nutrition* 2011;**94**(6):1442–50.

Hoogeveen E, Gemen E, Geleijnse M, Kusters R, Kromhout D, Giltay E. Effects of n-3 fatty acids on decline of kidney function after myocardial infarction: Alpha Omega Trial. *Nephrology, Dialysis, Transplantation* 2012;27:ii64. Hoogeveen EK, Geleijnse JM, Kromhout D, Giltay EJ. No effect of n-3 fatty acids on high-sensitivity C-reactive

No effect of n-3 fatty acids on high-sensitivity C-reactive protein after myocardial infarction: the Alpha Omega Trial. European Journal of Preventive Cardiology 2014;21(11): 1429–36.

Hoogeveen EK, Geleijnse JM, Kromhout D, Stijnen T, Gemen EF, Kusters R, et al. Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega Trial. *Clinical Journal of The American Society of Nephrology: CJASN* 2014;9(10):1676–83.

Kromhout D, Geleijnse JM, De Goede J, Oude Griep LM, Mulder BJ, De Boer MJ, et al. N-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. *Diabetes Care* 2011;**34**(12):2515–20.

* Kromhout D, Giltay EJ, Geleijnse JM. N-3 fatty acids and cardiovascular events after myocardial infarction. *New England Journal of Medicine* 2010;**363**(18):2015–26. NCT00127452. Alpha Omega Trial: study of omega-3

fatty acids and coronary mortality. clinicaltrials.gov/ct2/show/NCT00127452 (first posted 5 August 2005).

Bassey 2000-Post {published data only}

Bassey EJ, Littlewood JJ, Rothwell MC, Pye DW. Lack of effect of supplementation with essential fatty acids on bone mineral density in healthy pre- and postmenopausal women: two randomized controlled trials of Efacal v. calcium alone. *British Journal of Nutrition* 2000;**83**(6):629–35. PUBMED: 10911771]

Bassey 2000-Pre {published data only}

Bassey EJ, Littlewood JJ, Rothwell MC, Pye DW. Lack of effect of supplementation with essential fatty acids on bone mineral density in healthy pre- and postmenopausal women: two randomized controlled trials of Efacal v. calcium alone. *British Journal of Nutrition* 2000;**83**(6):629–35. PUBMED: 10911771]

Bates 1977 {published data only (unpublished sought but not used)}

* Bates D, Fawcett PR, Shaw DA, Weightman D. Trial of polyunsaturated fatty acids in non-relapsing multiple sclerosis. *British Medical Journal* 1977;**2**(6092):932–3. Dworkin RH, Bates D, Millar JH, Paty DW. Linoleic acid and multiple sclerosis: a reanalysis of three double-blind trials. *Neurology* 1984;**34**(11):1441–5.

Bates 1978 {published data only (unpublished sought but not used)}

* Bates D, Fawcett PR, Shaw DA, Weightman D. Polyunsaturated fatty acids in treatment of acute remitting multiple sclerosis. *British Medical Journal* 1978;**2**(6149): 1390–1.

Dworkin RH, Bates D, Millar JH, Paty DW. Linoleic acid and multiple sclerosis: a reanalysis of three double-blind trials. *Neurology* 1984;**34**(11):1441–5.

Bates 1989 {published data only (unpublished sought but not used)}

Bates D, Cartlidge NE, French JM, Jackson MJ, Nightingale S, Shaw DA, et al. A double-blind controlled trial of long chain n-3 polyunsaturated fatty acids in the treatment of multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 1989;**52**(1):18–22.

Black 1994 {published and unpublished data}

* Black HS, Herd JA, Goldberg LH, Wolf-JE J, Thornby JI, Rosen T, et al. Effect of a low-fat diet on the incidence of actinic keratosis. *New England Journal of Medicine* 1994; 330(18):1272–5.

Black HS, Thornby JI, Wolf-JE J, Goldberg LH, Herd JA, Rosen T, et al. Evidence that a low-fat diet reduces the occurrence of non-melanoma skin cancer. *International Journal of Cancer* 1995;**62**(2):165–9.

Jaax S, Scott LW, Wolf-JE J, Thornby JI, Black HS. General guidelines for a low-fat diet effective in the management and prevention of nonmelanoma skin cancer. *Nutrition and Cancer* 1997;**27**(2):150–6.

Brox 2001 {published and unpublished data}

Brox J, Olaussen K, Osterud B, Elvevoll EO, Bjornstad E, Brattebog G, et al. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. *Lipids* 2001;**36**(1):7–13.

DART fat 1989 {published and unpublished data}

Burr ML, Fehily AM. Fish and the heart. *Lancet* 1989;**ii**: 1450–2.

* Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;**2**(8666):757–61. Burr ML, Fehily AM, Rogers S, Welsby E, King S, Sandham S. Diet and reinfarction trial (DART): design, recruitment, and compliance. *European Heart Journal* 1989;**10**(6): 558–67.

Burr ML, Holliday RM, Fehily AM, Whitehead PJ. Haematological prognostic indices after myocardial infarction: evidence from the diet and reinfarction trial (DART). European Heart Journal 1992;13(2):166–70. Burr ML, Sweetham PM, Fehily AM. Diet and reinfarction [letter]. European Heart Journal 1994;15(8):1152–3. Fehily AM, Vaughan-Williams E, Shiels K, Williams AH, Horner M, Bingham G, et al. The effect of dietary advice on nutrient intakes: evidence from the diet and reinfarction trial (DART). Journal of Human Nutrition & Dietetics 1989; 2(4):225–5.

DIPP-Tokudome 2015 {published and unpublished data}

* Tokudome S, Kuriki K, Yokoyama Y, Sasaki M, Joh T, Kamiya T, et al. Dietary n-3/long-chain n-3 polyunsaturated fatty acids for prevention of sporadic colorectal tumors: a randomized controlled trial in polypectomized participants. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 2015; **94**:1–11. PUBMED: 25451556]

Tokudome S, Yokoyama Y, Kamiya T, Seno K, Okuyama H, Kuriki K, et al. Rationale and study design of dietary intervention in patients polypectomized for tumors of the colorectum. *Japanese Journal of Clinical Oncology* 2002;**32** (12):550–3. PUBMED: 12578906]

UMIN00000461. Dietary intervention in patients polypectomized for tumors of the colorectum. upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000000534 (date of disclosure 3 August 2006).

Dodin 2005 {published and unpublished data}

Dodin S, Cunnane SC, Masse B, Lemay A, Jacques H, Asselin G, et al. Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. *Nutrition (Burbank, Los Angeles County, Calif.)* 2008;**24**(1):23–30. PUBMED: 17981439]

* Dodin S, Lemay A, Jacques H, Legare F, Forest JC, Masse B. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebocontrolled clinical trial. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**(3):1390–7. PUBMED: 15613422]

Doi 2014 {published data only (unpublished sought but not used)}

Doi M, Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, et al. Clinical outcomes of early initiation of pure eicosapentaenoic acid supplement after percutaneous coronary intervention in patients with acute coronary

syndrome. *European Heart Journal* 2014;**35**(Abstract Supplement):1156.

* Doi M, Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. *International Journal of Cardiology* 2014; 176(3):577–82. PUBMED: 25305703]

Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, Tsukuda S, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. *International Journal of Cardiology* 2017;**228**:173–9. DOI: 10.1016/j.ijcard.2016.11.105

Nosaka K, Miyoshi T, Okawa K, Tsukuda S, Sogo M, Nishibe T, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. *Journal of the American College of Cardiology* 2016; **67**:573.

UMIN00016723. Clinical effect of early loading of eicosepentaenoic acid after percutaneous coronary intervention in patients with acute coronary syndrome: a prospective, open-labeled, randomized controlled clinical trial. upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi? recptno=R000019385 (date of disclosure 1 April 2015).

Dullaart 1992 {published and unpublished data}

Dullaart RP, Beusekamp BJ, Meijer S, Hoogenberg K, Van Doormaal JJ, Sluiter WJ. Long-term effects of linoleic-acidenriched diet on albuminuria and lipid levels in type 1 (insulin-dependent) diabetic patients with elevated urinary albumin excretion. *Diabetologia* 1992;**35**(2):165–72. PUBMED: 1547922]

EPIC-1 2008 {published and unpublished data}

* Feagan BG, Sandborn WJ, Mittmann U, Bar-Meir S, D'Haens G, Bradette M, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. *JAMA* 2008;**299**(14): 1690–7.

NCT00613197. EPANOVA in Crohn's disease, study 1 (EPIC-1). clinicaltrials.gov/ct2/show/NCT00613197 (first posted 12 February 2008).

EPIC-2 2008 {published and unpublished data}

* Feagan BG, Sandborn WJ, Mittmann U, Bar-Meir S, D'Haens G, Bradette M, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. *JAMA* 2008;**229**(14): 1690–7.

NCT00074542. An efficacy and safety study of omega-3 free fatty acids (Epanova) for the maintenance of symptomatic remission in subjects with Crohn's disease. clinicaltrials.gov/ct2/show/NCT00074542 (first posted 16 December 2003).

EPOCH 2011 {published and unpublished data}

ACTRN12607000278437. Older people, omega-3, and cognitive health [An 18 month study investigating the effects of long chain omega-3 polyunsaturated fatty acids supplementation on cognition and wellbeing in older people]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12607000278437 (date registered 24 May 2007).

Danthiir V, Burns NR, Nettelbeck T, Wilson C, Wittert G. The older people, omega-3, and cognitive health (EPOCH) trial design and methodology: a randomised, doubleblind, controlled trial investigating the effect of long-chain omega-3 fatty acids on cognitive ageing and wellbeing in cognitively healthy older adults. *Nutrition Journal* 2011;10: 117. PUBMED: 22011460]

* Danthiir V, Hosking D, Burns NR, Wilson C, Nettelbeck T, Calvaresi E, et al. Cognitive performance in older adults is inversely associated with fish consumption but not erythrocyte membrane n-3 fatty acids. *Journal of Nutrition* 2014;**144**(3):311–20. PUBMED: 24353345]

FAAT - Leaf 2005 {published and unpublished data}

* Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* 2005; **112**(18):2762–8.

NCT00004559. Fatty Acid Antiarrhythmia Trial (FAAT). clinicaltrials.gov/ct2/show/NCT00004559 (first posted 10 February 2000).

GLAMT 1993 {published data only (unpublished sought but not used)}

Keen H, Payan J, Allawi J, Walker J, Jamal GA, Weir AI, et al. Treatment of diabetic neuropathy with gamma-linolenic acid. *Diabetes Care* 1993;**16**(1):8–15.

HARP- Sacks 1995 {published and unpublished data}

NCT00000461. Harvard Atherosclerosis Reversibility Project (HARP). clinicaltrials.gov/ct2/show/NCT00000461 (first posted 28 October 1999).

Pasternak RC, Brown LE, Stone PH, Silverman DI, Gibson CM, Sacks FM. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. *Annals of Internal Medicine* 1996;**125**(7): 529–40. PUBMED: 8815751]

Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. *Lancet* 1994;**344**(8931):1182–6. PUBMED: 7934538

* Sacks FM, Stone PH, Gibson CM, Silverman DI, Rosner B, Pasternak RC. Controlled trial of fish oil for regression of human coronary atherosclerosis. *Journal of the American College of Cardiology* 1995;**25**(7):1492–8.

HERO-Tapsell 2009 {published and unpublished data}

ACTRN12607000600448. Healthy eating to reduce overweight in people with type 2 diabetes [The role of walnuts in satiety and energy balance in overweight individuals with type 2 diabetes mellitus].

www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=82353 (date registered 21 November 2007).

Tan SY. Dietary Manipulation and Weight Management [thesis]. Wollongong (Australia): School of Health Sciences, University of Wollongong, 2010.

* Tapsell LC, Batterham MJ, Teuss G, Tan SY, Dalton S, Quick CJ, et al. Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes. *European Journal of Clinical Nutrition* 2009;**63**(8):1008–15. PUBMED: 19352378]

Houtsmuller 1979 {published data only (unpublished sought but not used)}

Houtsmuller AJ, Van Hal-Ferwerda J, Zahn KJ, Henkes HE. Favourable influences of linoleic acid on the progression of diabetic micro- and macroangiopathy. *Nutrition and Metabolism* 1980;**24**(Suppl 1):105–18.

Houtsmuller AJ, Van Hal-Ferwerda J, Zahn KJ, Henkes HE. Influence of different diets on the progression of diabetic retinopathy. *Progress in Food Nutritition and Science* 1980;4(5):41–6.

* Houtsmuller AJ, Zahn KJ, Henkes HE. Unsaturated fats and progression of diabetic retinopathy. *Documenta Ophthalmologia* 1979;**48**(2):363–71.

Kumar 2012 {published data only (unpublished sought but not used)}

* Kumar S, Sutherland F, Morton JB, Lee G, Morgan J, Wong J, et al. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. *Heart Rhythm* 2012;9(4):483–91. DOI: 10.1016/j.hrthm.2011.11.034 NCT00232219. Use of fish oils to reduce recurrence of atrial fibrillation following DC cardioversion. clinicaltrials.gov/ct2/show/NCT00232219 (first posted 4 October 2005).

Kumar 2013 {published data only}

* Kumar S, Sutherland F, Stevenson I, Lee JM, Garg ML, Sparks PB. Effects of long-term omega-3 polyunsaturated fatty acid supplementation on paroxysmal atrial tachyarrhythmia burden in patients with implanted pacemakers: results from a prospective randomised study. *International Journal of Cardiology* 2013;**168**(4):3812–7. PUBMED: 23890856]

NCT00232245. Use of fish oils to reduce the frequency and duration of episodes of atrial fibrillation in patients with paroxysmal atrial fibrillation. clinicaltrials.gov/ct2/show/NCT00232245 (first posted 4 October 2005).

Ley 2004 {published and unpublished data}

* Ley SJ, Metcalf PA, Scragg RKR, Swinburn BA. Long-term effects of a reduced fat diet intervention on cardiovascular disease risk factors in individuals with glucose intolerance. *Diabetes Research and Clinical Practice* 2004;63:103–12. Swinburn BA, Metcalf PA, Ley SJ. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care* 2001;24(4):619–24. Swinburn BA, Woollard GA, Chang EC, Wilson MR. Effects of reduced-fat diets consumed ad libitum on intake of nutrients particularly antioxidant vitamins. *Journal of the American Dietetic Association* 1999;99(11):1400–5.

MARINA - Sanders 2011 {published and unpublished data}

Al-Hilal M, Alsaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TA, et al. Genetic variation at the FADS1-FADS2 gene locus influences delta-5 desaturase activity and LC-PUFA proportions after fish oil supplement. *Journal of Lipid Research* 2013;**54**(2):542–51. PUBMED: 23160180] AlSaleh A, Maniou Z, Lewis FJ, Hall WL, Sanders TA, O'Dell SD. Interaction between a CSK gene variant and fish oil intake influences blood pressure in healthy adults. *Journal of Nutrition* 2014;**144**(3):267–72. PUBMED: 24401815]

Alsaleh A, Crepostnaia D, Maniou Z, Lewis FJ, Hall WL, Sanders TA, et al. Adiponectin gene variant interacts with fish oil supplementation to influence serum adiponectin in older individuals. *Journal of Nutrition* 2013;**143**(7): 1021–7. PUBMED: 23658423]

Hall WL, Hay G, Maniou Z, Seed PT, Chowienczyk PJ, Sanders TA. Effect of low doses of long chain n-3 polyunsaturated fatty acids on sleep-time heart rate variability: a randomized, controlled trial. *International Journal of Cardiology* 2013;**168**:4439–42.

ISRCTN66664610. Vascular effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA): the MARINA study. www.isrctn.com/ISRCTN66664610 (date assigned 17 December 2008).

Pinto AM, Hall WL, Sanders TAB. Effect of low doses of long chain n-3 PUFA intake on daytime heart rate variability: results from the MARINA study. *European Journal of Preventive Cardiology* 2015;1:S146.

Proudman S, Spargo L, Hall C, McWilliams L, Lee A, Maureen R, et al. Fish oil in rheumatoid arthritis: a randomised, double blind trial comparing high dose with low dose. *Internal Medicine Journal* 2012;42:2–3.

* Sanders TA, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. *American Journal of Clinical Nutrition* 2011;94(4):973–80. PUBMED: 21865334]

Sanders TAB, Chowienczyk PJ, Hall W, Lewis F, Seed P,

Maniou Z, et al. The influences of increasing intakes of

EPA and DHA on vascular function and risk factors for

cardiovascular disease. Food Standards Agency Project

McIllmurray 1987 {published data only (unpublished sought but not used)}

McIllmurray MB, Turkie W. Controlled trial of gamma linolenic acid in Duke's C colorectal cancer. *BMJ (Clinical Research Ed.)* 1987;**294**(6582):1260 (Erratum in: BMJ 1987;295(6596):475).

Mendis 2001 {published data only (unpublished sought but not used)}

Mendis S, Samarajeewa U, Thattil RO. Coconut fat and serum lipoproteins: effects of partial replacement with unsaturated fats. *British Journal of Nutrition* 2001;**85**(5): 583–9.

Mita 2007 {published data only}

N02041. Final Report 2011.

Mita T, Watada H, Ogihara T, Nomiyama T, Ogawa O, Kinoshita J, et al. Eicosapentaenoic acid reduces the

progression of carotid intima-media thickness in patients with type 2 diabetes. *Atherosclerosis* 2007;**191**(1):162–7.

MRC 1968 {published and unpublished data}

Ederer F, Leren P, Turpeinen O, Frantz ID Jr. Cancer among men on cholesterol lowering diets: experience of five clinical trials. *Lancet* 1971;**2**:203–6.

Heady JA. Are PUFA harmful?. *British Medical Journal* 1974;**1**(898):115–6.

* MRC. Controlled trial of soya-bean oil in myocardial infarction; report of a medical research committee to the Medical Research Council. *Lancet* 1968;**2**(570):693–9.

NDHS Faribault 1968 {published data only}

The National Diet-Heart Study. Nutrition Reviews 1968; Vol. 26, issue 5:133-6.

* The National Diet-Heart Study final report. Circulation 1968; Vol. 37, issue II:1–428.

Baker BM, Frantz ID Jr, Keys A, Kinsell LW, Page IH, Stamler J, et al. The National Diet-Heart Study: an initial report. *JAMA* 1963;**185**:105–6.

Brown HB. The National Diet Heart Study - implications for dietitians and nutritionists. *Journal of the American Dietetic Association* 1968;**52**:279–87.

Ederer F, Leren P, Turpeinen O, Frantz ID Jr. Cancer among men on cholesterol-lowering diets: experience from five clinical trials. *Lancet* 1971;**298**(7717):203–6.

Page IH, Brown HB. Some observations on the National Diet-Heart Study. *Circulation* 1968;**37**:313–5.

NDHS Open 1st 1968 {published data only}

The National Diet-Heart Study. Nutrition Reviews 1968; Vol. 26, issue 5:133–6.

* The National Diet-Heart Study final report. Circulation 1968; Vol. 37, issue II:1–428.

Baker BM, Frantz ID Jr, Keys A, Kinsell LW, Page IH, Stamler J, et al. The National Diet-Heart Study: an initial report. *JAMA* 1963;**185**:105–6.

Brown HB. The National Diet Heart Study - implications for dietitians and nutritionists. *Journal of the American Dietetic Association* 1968;**52**:279–87.

Ederer F, Leren P, Turpeinen O, Frantz ID Jr. Cancer among men on cholesterol-lowering diets: experience from five clinical trials. *Lancet* 1971;**298**(7717):203–6.

Page IH, Brown HB. Some observations on the National Diet-Heart Study. *Circulation* 1968;**37**:313–5.

Nodari 2011 AF {published data only (unpublished sought but not used)}

NCT01198275. N-3 polyunsaturated fatty acids (PUFAs) in the prevention of atrial fibrillation. clinicaltrials.gov/ct2/show/NCT01198275 (first posted 21 July 2011).

* Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, et al. N-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. *Circulation* 2011;**124**(10):1100–6. PUBMED: 21844082]

Nodari 2011 HF {published and unpublished data}

NCT01223703. PUFAs and left ventricular function in heart failure (CS-PUFA-02). clinicaltrials.gov/ct2/show/

NCT01223703 (first posted 19 October 2010). NCT01223703. PUFAs and left ventricular function in heart failure (CS-PUFA-02). clinicaltrials.gov/ct2/show/ results/NCT01223703 (first posted 19 October 2010). Nodari S, Triggiani M, Berlinghieri N, Milesi G, Foresti A, Gheorghiade M, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in heart failure patients. European Heart Journal 2010;31:850. * Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. Journal of the American College of Cardiology 2011;57(7):870-9. Nodari S, Triggiani M, Campia U, Zhao L, Manerba A, Milesi G, et al. Plasma levels of n-3 polyunsaturated fatty acids and risk of hospitalization in patients with nonischemic cardiomyopathy. Circulation 2012;126(21 SUPPL 1):17431.

Nye 1990 {published data only}

Ilsey CDJ, Nye ER, Sutherland W, Ram J, Ablett MB. Randomised placebo controlled trial of MAXEPA and aspirin/persantin after successful coronary angioplasty.
Australian & New Zealand Journal of Medicine 1987;17:559.

* Nye ER, Ablett MB, Robertson MC, Ilsley CD, Sutherland WH. Effect of eicosapentaenoic acid on restenosis rate, clinical course and blood lipids in patients after percutaneous transluminal coronary angioplasty.
Australian and New Zealand Journal of Medicine 1990;20 (4):549–52.

ORL 2013 {published data only (unpublished sought but not used)}

NCT01350999. Long-term efficacy and safety study of TAK-085 in participants with hypertriglyceridemia. clinicaltrials.gov/ct2/show/NCT01350999 (first posted 10 May 2011).

* Tatsuno I, Saito Y, Kudou K, Ootake J. Long-term safety and efficacy of TAK-085 in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: the omega-3 fatty acids randomized long-term (ORL) study. *Journal of Clinical Lipidology* 2013;7(6):615–25. PUBMED: 24314359]

PREDIMED 2013 {published data only (unpublished sought but not used)}

PREDIMED study - Mediteranian diet in the primary prevention of cardiovascular disease: research protocol, version 1. www.predimed.es/uploads/8/0/5/1/8051451/_lestr_protocol_olf.pdf (accessed prior to 11 April 2018). Alvarez-Perez J, Sanchez-Villegas A, Diaz-Benitez EM, Ruano-Rodriguez C, Corella D, Martinez-Gonzalez MA, et al. Influence of a Mediterranean dietary pattern on body fat distribution: results of the PREDIMED-Canarias intervention randomized trial. *Journal of the American College of Nutrition* 2016;35(6):1–13.

Babio N, Toledo E, Estruch R, Ros E, Martinez-Gonzalez MA, Castaner O, et al. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. CMAJ Canadian Medical Association Journal 2014;186(17): E649-57.

Barcelo F, Perona JS, Prades J, Funari SS, Gomez-Gracia E, Conde M, et al. Mediterranean-style diet effect on the structural properties of the erythrocyte cell membrane of hypertensive patients: the Prevencion con Dieta Mediterranea Study. *Hypertension* 2009;54(5):1143–50. Bullo M, Amigo-Correig P, Marquez-Sandoval F, Babio N, Martinez-Gonzalez MA, Estruch R, et al. Mediterranean diet and high dietary acid load associated with mixed nuts: effect on bone metabolism in elderly subjects. *Journal of the American Geriatrics Society* 2009;57(10):1789–98.

Casas R, Sacanella E, Urpi-Sarda M, Chiva-Blanch G,

Casas R, Sacanella E, Urpi-Sarda M, Chiva-Blanch G, Ros E, Martinez-Gonzalez MA, et al. The effects of the Mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. *PloS One* 2014;9(6):e100084.

Casas RM, Urpi-Sarda M, Chiva-Blanch G, Valderas-Martinez P, Arranz S, Roth I, et al. Inhibition of circulating immune cells related to atherogenesis intervention after 1, 3 and 5 years with Mediterranean diet. *Annals of Nutrition and Metabolism* 2013;**62**:43–4.

Cohen J, Rimm EB, Martinez-Gonzalez MA, Salas-Salvado J, Covas MI, Corella D, et al. The association between obesity status and long-term adherence to Mediterranean diet in the PREDIMED trial. *Circulation* 2013;**127**(12 Meeting Abstracts):AP098.

Damasceno NR, Sala-Vila A, Cofan M, Perez-Heras AM, Fito M, Ruiz-Gutierrez V, et al. Mediterranean diet supplemented with nuts reduces waist circumference and shifts lipoprotein subfractions to a less atherogenic pattern in subjects at high cardiovascular risk. *Atherosclerosis* 2013; **230**(2):347–53.

Domenech M, Estruch R, Ros E, Coca A. Effect of the Mediterranean diet on blood pressure: the ambulatory blood pressure substudy (Predimed-ABPM). *Journal of Hypertension* 2010;**28**:e373.

Domenech M, Roman P, Lapetra J, Garcia de la Corte FJ, Sala-Vila A, de la Torre R, et al. Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: one-year randomized, clinical trial. *Hypertension* 2014;**64**(1):69–76.

* Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *New England Journal of Medicine* 2013;**368**(14):1279-90 (Erratum in: New England Journal of Medicine 2014;370(9):886). DOI: 10.1056/NEJMoa1200303

Estruch R, Ros E, Salas-Salvadó J, Covas M, Corella D, Arós F, et al. Retraction and republication: Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013; 368:1279-90. *NEJM* 2018;378:25. DOI: 10.1056/NEJMc1805501

Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts [this is a republication of primary paper

Estruch 2013]. New England Journal of Medicine 2018;378: e34. DOI: 10.1056/NEJMoa1800389
ISRCTN35739639. Effects of Mediterranean diet on the primary prevention of cardiovascular disease. www.isrctn.com/ISRCTN35739639 (date assigned 5 October 2005).

Martínez-González MÁ, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, et al. Cohort profile: design and methods of the PREDIMED study. *International Journal of Epidemiology* 2012;**41**(2):377–85. DOI: 10.1093/ije/dyq250

Papadaki A, Martínez-González MÁ, Alonso-Gómez A, Rekondo J, Salas-Salvadó J, Corella D, et al. Mediterranean diet and risk of heart failure: results from the PREDIMED randomized controlled trial. *European Journal of Heart Failure* 2017;**19**(9):1179–85. DOI: 10.1002/ejhf.750 Razquin C, Martinez JA, Martinez-Gonzalez MA, Mitjavila MT, Estruch R, Marti A. A 3 years follow-up of a Mediterranean diet rich in virgin olive oil is associated with high plasma antioxidant capacity and reduced body weight gain. *European Journal of Clinical Nutrition* 2009;**63**(12): 1387–93.

Ruiz-Canela M, Estruch R, Corella D, Salas-Salvado J, Martinez-Gonzalez MA. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA* 2014;**311**(4):415–7.

Sala-Vila A, Romero-Mamani ES, Gilabert R, Nunez I, de la Torre R, Corella D, et al. Changes in ultrasound-assessed carotid intima-media thickness and plaque with a Mediterranean diet: a substudy of the PREDIMED trial. Arteriosclerosis, Thrombosis & Vascular Biology 2014;34(2): 439–45.

Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011;34(1):14–9. Salas-Salvado J, Bullo M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Annals of Internal Medicine* 2014;160(1):1–10. Salas-Salvado J, Fernandez-Ballart J, Ros E, Martinez-Gonzalez MA, Fito M, Estruch R, et al. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Archives of Internal Medicine* 2008;168 (22):2449–58.

Sanchez-Villegas A, Martinez-Gonzalez MA, Estruch R, Salas-Salvado J, Corella D, Covas MI, et al. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. *BMC Medicine* 2013;11:208.

Sola R, Fito M, Estruch R, Salas-Salvado J, Corella D, de la Torre R, et al. Effect of a traditional Mediterranean diet on apolipoproteins B, A-I, and their ratio: a randomized, controlled trial. *Atherosclerosis* 2011;218(1):174–80.

Toledo E, Hu FB, Estruch R, Buil-Cosiales P, Corella D, Salas-Salvado J, et al. Effect of the Mediterranean diet on

blood pressure in the PREDIMED trial: results from a randomized controlled trial. *BMC Medicine* 2013;11:207. Toledo E, Salas-Salvado J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED Trial: a randomized clinical trial. *JAMA Internal Medicine* 2015;175(11):1752–60. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Internal Medicine* 2015;175(7):1094–103.

Proudman 2015 {published and unpublished data}

ACTRN12613000579796. Fish oil in recent onset rheumatoid arthritis: High versus low dose fish oil on a background of dose-responsive combination disease-modifying anti-rheumatic drugs [Fish oil in anti-inflammatory doses in recent onset rheumatoid arthritis: a randomized, double-blind controlled trial within algorithm-based drug use with DMARD use as the primary outcome]. www.anzctr.org.au/Trial/Registration/ TrialReview.aspx?id=364265 (date registered 23 May 2013). Proudman S, Spargo L, Hall C, McWilliams L, Lee A, Maureen R, et al. Fish oil in rheumatoid arthritis: a randomised, double blind trial comparing high dose with low dose. Internal Medicine Journal 2012;42(Suppl 1):2-3. * Proudman SM, Cleland LG, Metcalf RG, Sullivan TR, Spargo LD, James MJ. Plasma n-3 fatty acids and clinical outcomes in recent-onset rheumatoid arthritis. British Journal of Nutrition 2015;114(6):885-90. PUBMED: 262836571

Proudman SM, James MJ, Spargo LD, Metcalf RG, Sullivan TR, Rischmueller M, et al. Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. *Annals of the Rheumatic Diseases* 2015;74(1):89–95. PUBMED: 24081439]

Puri 2005 {published and unpublished data}

ISRCTN79170611. A multicentre, multinational, double blind, randomised, parallel group, placebocontrolled study of ethyl-eicosapentaenoate (EPA) in patients with Huntington's disease (HD). doi.org/10.1186/ISRCTN79170611 (date assigned 3 February 2003).

* Puri BK, Leavitt BR, Hayden MR, Ross CA, Rosenblatt A, Greenamyre JT, et al. Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial. Neurology 2005;65(2):286–92.

Raitt 2005 {published data only (unpublished sought but not used)}

NCT00004558. Antiarrhythmic effects of n-3 fatty acids. clinicaltrials.gov/ct2/show/NCT00004558 (first posted 10 February 2000).

* Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA* 2005;**293**(23):2884–91.

Rose 1965 {published data only}

Rose GA, Thomson WB, Williams RT. Corn oil in treatment of ischaemic heart diseases. *British Medical Journal* 1965;1(5449):1531–3. PUBMED: 14288105]

Rossing 1996 {published and unpublished data}

Myrup B, Rossing P, Jensen T, Parving HH, Holmer G, Gram J, et al. Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic patients with diabetic nephropathy. Scandinavian Journal of Clinical & Laboratory Investigation 2001;61(5):349–56.

* Rossing P, Hansen BV, Nielsen FS, Myrup B, Holmer G, Parving HH. Fish oil in diabetic nephropathy. *Diabetes Care* 1996;**19**(11):1214–9.

Simon 1997 {published and unpublished data}

Djuric Z, Heilbrun LK, Reading BA, Boomer A, Valeriote FA, Martino S. Effects of a low fat diet on levels of oxidative damage to DNA in human peripheral nucleated blood cells. *Journal of the National Cancer Institute* 1991;83(11):766–9. Djuric Z, Martino S, Heilbrun LK, Hart RW. Dietary modulation of oxidative DNA damage. *Advances In Experimental Medicine and Biology* 1994;354:71–83. Kasim SE, Martino S, Kim P-N, Khilnani S, Boomer A, Depper J, et al. Dietary and anthropometric determinants of plasma lipoproteins during a long-term low-fat diet in healthy women. *American Journal of Clinical Nutrition* 1993;57:146–53.

* Simon MS, Heilbrun LK, Boomer A, Kresge C, Depper J, Kim PN, et al. A randomised trial of a low-fat dietary intervention in women at high risk for breast cancer. Nutrition and Cancer 1997;27(2):136–42.

Sydney Diet-Heart 1978 {published and unpublished data}

Blacket RB, Leelarthaepin B, McGilchrist C, Palmer AJ, Woodhill JM. The synergistic effect of weight loss and changes in dietary lipids on the serum cholesterol of obese men with hypercholesterolaemia: implications for prevention of coronary heart disease. *Australian and New Zealand Journal of Medicine* 1979;9:521–9.

Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ* 2013;346:e8707 (Erratum in: BMJ 2013;346:f903).

* Woodhill JM, Palmer AJ, Leelarthaepin B, McGilchrist C, Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Advances in Experimental Medicine and Biology* 1978;**109**:317–30.

Veterans Admin 1969 {published data only}

Dayton S, Hashimoto S, Dixon W, Pearce ML. Composition of lipids in human serum and adipose tissue during prolonged feeding of a diet high in unsaturated fat. *Journal of Lipid Research* 1966;7:103–11.

Dayton S, Hashimoto S, Pearce ML. Adipose tissue linoleic acid as a criterion of adherence to a modified diet. *Journal of Lipid Research* 1967;**8**:508–10.

Dayton S, Hashimoto S, Pearce ML. Influence of a diet

high in unsaturated fat upon composition of arterial tissue and atheromata in man. *Circulation* 1965;**32**:911–24.

Dayton S, Hashimoto S, Rosenblum D, Pearce M. Vitamin E status of humans during prolonged feeding of unsaturated fats. *Journal of Laboratory and Clinical Medicine* 1965;**65** (5):739–47

Dayton S, Pearce ML. Diet and atherosclerosis. *Lancet* 1970;**1**(644):473–4.

Dayton S, Pearce ML. Diet and cardiovascular diseases. *Lancet* 1969;1(584):51–2.

Dayton S, Pearce ML. Diet high in unsaturated fat: a controlled clinical trial. *Minnesota Medicine* 1969;**1969**: 1237–42.

Dayton S, Pearce ML. Prevention of coronary heart disease and other complications of atherosclerosis by modified diet. *American Journal of Medicine* 1969;**46**:751–62.

Dayton S, Pearce ML. Trial of unsaturated-fat diet. *Lancet* 1968;**2**(581):1296–7.

Dayton S, Pearce ML, Goldman H, Harnish A, Plotkin D, Shickman M, et al. Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. *Lancet* 1968;**2**(577):1060–2.

* Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomayasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 1969;**15**(1, Suppl 2):II–1-63.

Dayton S, Pearce ML, Hashimoto S, Fakler LJ, Hiscock E, Dixon WJ. A controlled clinical trial of a diet high in unsaturated fat. *New England Journal of Medicine* 1962; **266**:1017–23.

Ederer F, Leren P, Turpeinen O, Frantz ID Jr. Cancer among men on cholesterol-lowering diets: experience from five clinical trials. *Lancet* 1971;**298**(7717):203–6.

Hiscock E, Dayton S, Pearce ML, Hashimoto S. A palatable diet high in unsaturated fat. *Journal of the American Dietetic Association* 1962;**40**:427–31.

Pearce ML, Dayton S. Incidence of cancer in men on a diet high in polyunsaturated fat. *Lancet* 1971;**1**(697):464–7. Sturdevant RA, Pearce ML, Dayton S. Increased prevalence of cholelithiasis in men ingesting a serum-cholesterol-lowering diet. *New England Journal of Medicine* 1973;**288**

Tompkins MJ, Dayton S, Pearce ML. Effect of long-term feeding of various fats on whole blood clotting times in men. *Journal of Laboratory and Clinical Medicine* 1964;**64** (5):763–72.

Vijayakumar 2014 {published and unpublished data}

Nandakumar S, Vijayakumar M, Krishnan S. Coconut oil vs sunflower oil in atherosclerosis: challenges in dietary intervention. *Indian Heart Journal* 2014;**66**:S11.

* Vijayakumar M, Krishnaan S, Sundram KR, Vasudevan DM, Nandakumar S. What oil in patients with established coronary artery disease: outcomes of two year dietary intervention with coconut oil & sunflower oil. *Indian Heart Journal* 2014;**66**:S12.

Vijayakumar M, Vasudevan DM, Sundaram KR, Krishnan S, Vaidyanathan K, Nandakumar S, et al. A randomized

study of coconut oil versus sunflower oil on cardiovascular risk factors in patients with stable coronary heart disease. *Indian Heart Journal* 2016;**68**:498–506. DOI: 10.1016/j.ihj.2015.10.384

WAHA - Ros 2016 {published and unpublished data}

Bitok E, Jaceldo-Siegl K, Rajaram S, Serra-Mir M, Roth I, Feitas-Simoes T, et al. Favourable nutrient intake and displacement with long-term walnut supplementation among elderly: results of a randomised trial. *British Journal of Nutrition* 2017;**118**(3):201–9. DOI: 10.1017/S0007114517001957

Bitok E, Rajaram S, Ros E, Kazzi N, Huey L, Jaceldo K, et al. Does a daily walnut supplement given for a year result in body weight gain? *FASEB Journal* 2016;**30**(1):1157.

Huey L, Bitok E, Kazzi N, Sirirat R, Haddad Tabrizi S, Ros E, et al. Dietary compliance of walnut or no walnut intake in a 1-year randomized intervention trial among free-living elderly in the Walnuts and Healthy Aging Study (WAHA). FASEB Journal 2016; Vol. 30:1157.10.

NCT01634841. Walnuts and Healthy Aging (WAHA). clinicaltrials.gov/ct2/show/NCT01634841 (first posted 6 July 2012).

Rajaram S, Valls-Pedret C, Cofan M, Sabate J, Serra-Mir M, Perez-Heras AM, et al. The Walnuts and Healthy Aging Study (WAHA): protocol for a nutritional intervention trial with walnuts on brain aging. *Frontiers in Aging Neuroscience* 2016;**8**:333. PUBMED: 28119602]

* Ros E, Rajaram S, Sala-Vila A, Serra-Mir M, Valls-Pedret C, Cofan M, et al. Effect of a 1-year walnut supplementation on blood lipids among older individuals: findings from the walnuts and healthy aging (WAHA) study. *FASEB Journal* 2016;**30**(1 Suppl):293–4.

WELCOME 2015 {published and unpublished data}

Bhatia L, Scorletti E, Curzen N, Clough GF, Calder PC, Byrne CD. Improvement in non-alcoholic fatty liver disease severity is associated with a reduction in carotid intimamedia thickness progression. *Atherosclerosis* 2016;**246**: 13–20. PUBMED: 26748347]

Byrne CD, Targher G. Ectopic fat, insulin resistance, and nonalcoholic fatty liver disease: implications for cardiovascular disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2014;**34**(6):1155–61. PUBMED: 247434281

Byrne CD, Targher G. Time to replace assessment of liver histology with MR-based imaging tests to assess efficacy of interventions for nonalcoholic fatty liver disease. Gastroenterology 2016; Vol. 150, issue 1:7–10. PUBMED: 26602219]

Clough GF, McCormick KG, Scorletti E, Bhatia L, Calder PC, Griffin MJ, et al. Higher body fat percentage is associated with enhanced temperature perception in NAFLD: results from the randomised Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with OMacor thErapy trial (WELCOME) trial. *Diabetologia* 2016;59(7):1422–9. PUBMED: 27106721]

* McCormick KG, Scorletti E, Bhatia L, Calder PC, Griffin MJ, Clough GF, et al. Impact of high dose n3 polyunsaturated fatty acid treatment on measures of microvascular function and vibration perception in non-alcoholic fatty liver disease: results from the randomised WELCOME trial. *Diabetologia* 2015;**58**(8):1916–25. PUBMED: 26021488

NCT00760513. Treatment of non alcoholic fatty liver disease with n-3 fatty acids. clinicaltrials.gov/ct2/show/ NCT00760513 (first posted 26 September 2008). Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Calder PC, et al. Design and rationale of the WELCOME trial: a randomised, placebo controlled study to test the efficacy of purified long chainomega-3 fatty acid treatment in non-alcoholic fatty liver disease. *Contemporary Clinical Trials* 2014;37(2):301-11 (Erratum in: Contemporary Clinical Trials 2014 May;38(1):156). PUBMED: 24556343]

Scorletti E, West AL, Bhatia L, Hoile SP, McCormick KG, Burdge GC, et al. Treating liver fat and serum triglyceride levels in NAFLD, effects of PNPLA3 and TM6SF2 genotypes: results from the WELCOME trial. *Journal of Hepatology* 2015;**63**(6):1476–83. PUBMED: 26272871] Targher G, Byrne CD. Clinical review: nonalcoholic fatty liver disease: a novel cardiometabolic risk factor for type 2 diabetes and its complications. *Journal of Clinical Endocrinology and Metabolism* 2013;**98**(2):483–95. PUBMED: 23293330]

WINS 2006 {published and unpublished data}

Chlebowski RT, Blackburn GL, Buzzard IM, Rose DP, Martino S, Khandekar JD, et al. Adherence to a dietary fat intake reduction program in postmenopausal women receiving therapy for early breast cancer. The Women's Intervention Nutrition Study. *Journal of Clinical Oncology* 1993;**11**(11):2072–80.

* Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the women's intervention nutrition study. *JNCI Journal of the National Cancer Institute* 2006;**98**(24):1767–76.

Chlebowski RT, Rose DP, Buzzard IM, Blackburn GL, York M, Insull W, et al. Dietary fat reduction in adjuvant breast cancer therapy: current rationale and feasibility issues. *Adjuvant. The Cancer Journal* 1990;**6**:357–63.

Hoy MK, Winters BL, Chlebowski RT, Papoutsakis C, Shapiro A, Lubin MP, et al. Implementing a low-fat eating plan in the Women's Intervention Nutrition Study. *Journal of the American Dietetic Association* 2009;**109**(4):688–96. Rose DP, Chlebowski RT, Connolly JM, Jones LA, Wynder EL. Effects of tamoxifen adjuvant therapy and a low-fat diet on serum binding proteins and estradiol bioavailability in postmenopausal breast cancer patients. *Cancer Research* 1992;**52**:5386–90.

Rose DP, Connolly JM, Chlebowski RT, Buzzard IM, Wynder EL. The effects of a low-fat dietary intervention and tamoxifen adjuvant therapy on the serum estrogen and sex hormone-binding globulin concentrations of postmenopausal breast cancer patients. *Breast Cancer*

Research & Treatment 1993;27(3):253–62. Wynder EL, Cohen LA, Winters BL. The challenges of assessing fat intake in cancer research investigations. *Journal of the American Dietetic Association* 1997;97(7 Suppl):S5–8.

References to studies excluded from this review

ADCS-Quinn 2010 {published data only}

Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *JAMA* 2010;**304**(17):1903–11.

AFFORD 2014 {published data only}

* Nigam A, Talajic M, Roy D, Nattel S, Lambert J, Nozza A, et al. Fish oil for the reduction of atrial fibrillation recurrence, inflammation, and oxidative stress. *Journal of the American College of Cardiology* 2014;**64**(14):1441–8. Nigam A, Talajic M, Roy D, Nattel S, Lambert J, Nozza A, et al. Multicentre trial of fish oil for the reduction of atrial fibrillation recurrence, inflammation and oxidative stress: the Atrial Fibrillation Fish Oil Research Study. *Canadian Journal of Cardiology* 2013;**1**:S383.

AlphaOmega - EPA+DHA {published and unpublished data}

Brouwer IA, Geleijnse JM, Klaasen VM, Smit LA, Giltay EJ, De Goede J, et al. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the alpha omega trial. *PLoS One* 2013;**8**(12): e81519.

Eussen SR, Geleijnse JM, Giltay EJ, Rompelberg CJ, Klungel OH, Kromhout D. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. *European Heart Journal* 2012;**33**(13):1582–8.

Geleijnse J, Giltay E, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's & Dementia 2011;1:S512.

Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. *Alzheimer's & Dementia* 2012;8(4):278–87. Geleijnse JM, Giltay EJ, Schouten EG, De Goede J, Oude Griep LM, Teitsma-Jansen AM, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: design and baseline characteristics of the Alpha Omega Trial. *American Heart Journal* 2010;159(4):539–46. DOI: 10/1016/j.ahj.2009.12.033

Giltay EJ, Geleijnse JM, Heijboer AC, De Goede J, Oude Griep LM, Blankenstein MA, et al. No effects of n-3 fatty acid supplementation on serum total testosterone levels in older men: the Alpha Omega Trial. *International Journal of Andrology* 2012;35(5):680–7.

Giltay EJ, Geleijnse JM, Kromhout D. Effects of n-3 fatty acids on depressive symptoms and dispositional optimism after myocardial infarction. *American Journal of Clinical Nutrition* 2011;**94**(6):1442–50.

Hoogeveen E, Gemen E, Geleijnse M, Kusters R, Kromhout D, Giltay E. Effects of n-3 fatty acids on decline of kidney function after myocardial infarction: Alpha Omega trial. *Nephrology Dialysis Transplantation* 2012;**27**:ii64.

Hoogeveen EK, Geleijnse JM, Kromhout D, Giltay EJ. No effect of n-3 fatty acids on high-sensitivity C-reactive protein after myocardial infarction: the Alpha Omega trial. *European Journal of Preventive Cardiology* 2014;**21**(11): 1429–36.

Hoogeveen EK, Geleijnse JM, Kromhout D, Stijnen T, Gemen EF, Kusters R, et al. Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega trial. *Clinical Journal of The American Society of Nephrology: CJASN* 2014;9(10):1676–83.

Kromhout D, Geleijnse JM, De Goede J, Oude Griep LM, Mulder BJ, De Boer MJ, et al. N-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. *Diabetes Care* 2011;**34**(12):2515–20.

* Kromhout D, Giltay EJ, Geleijnse JM. N-3 fatty acids and cardiovascular events after myocardial infarction. *New England Journal of Medicine* 2010;**363**(18):2015–26.

AREDS2 2014 {published and unpublished data}

* Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton CB, Hsia J, et al. Effect of long-chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA Internal Medicine* 2014;174(5):763–71.

Chew EY, Clemons T, SanGiovanni JP, Danis R, Domalpally A, McBee W, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology* 2012;**119**(11): 2282–9.

Chew EY, Clemons TE. In reply: making sense of the evidence from the age-related eye disease study 2 randomized clinical trial. *JAMA Ophthalmology* 2014;**132** (8):1031–2.

Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS, et al. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial. *JAMA* 2015;**314**(8):791–801.

Chew EY, Clemons TE, SanGiovanni JP, Danis RP, Ferris FL III, Elman MJ, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmology* 2014;**132**(2):142–9.

Chew EY, SanGiovanni JP, Ferris FL, Wong WT, Agron E, Clemons TE, et al. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. *JAMA Ophthalmology* 2013;**131**(7):843–50.

Huynh N, Nicholson BP, Agron E, Clemons TE, Bressler SB, Rosenfeld PJ, et al. Visual acuity after cataract surgery in patients with age-related macular degeneration: age-

related eye disease study 2 report number 5. *Ophthalmology* 2014;**121**(6):1229–36.

ASCEND {unpublished data only}

Bowman L, Aung T, Haynes R, Armitage J. ASCEND: design and baseline characteristics of a large randomised trial in diabetes. *Diabetes* 2012;**61**:A556–7.

Azadbakht 2007 {published and unpublished data}

Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Better dietary adherence and weight maintenance achieved by a long-term moderate fat diet. *British Journal of Nutrition* 2007;**97**:399–404.

Baldassarre 2006 {published data only}

Baldassarre D, Amato M, Eligini S, Barbieri SS, Mussoni L, Frigerio B, et al. Effect of n-3 fatty acids on carotid atherosclerosis and haemostasis in patients with combined hyperlipoproteinemia: a double-blind pilot study in primary prevention. *Annals of Medicine* 2006;**38**(5):367–75. DOI: 10.1080/07853890600852880

Berson 2004 {published data only}

* Berson EL, Rosner B, Sandberg MA, Weigel-DiFranco C, Moser A, Brockhurst RJ, et al. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. *Archives of Ophthalmology* 2004:**122**(9):1297–305.

Berson EL, Rosner B, Sandberg MA, Weigel-DiFranco C, Moser A, Brockhurst RJ, et al. Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment: subgroup analyses. *Archives of Ophthalmology* 2004;**122**(9):1306–14.

Caldwell 2011 {published data only}

Argo CK, Patrie JT, Lackner C, Henry TD, de Lange EE, Weltman AL, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. *Journal of Hepatology* 2015;**62**(1):190–7. PUBMED: 25195547]

* Caldwell SH, Argo CK, Henry TD, Lackner C, Pramoonjago P, Weltman AL, et al. Dissociated histological and metabolic effects of omega-e (3000 mg/d) versus placebo with both exercise and diet in a double-blind randomized controlled trial of NASH. Journal of Hepatology 2011; Vol. 54:S8.

DART 2 - Burr 2003 {published and unpublished data}

* Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *European Journal of Clinical Nutrition* 2003;57(2):193–200. Ness AR, Ashfield-Watt PAL, Whiting JM, Smith GD, Hughes J, Burr ML. The long-term effect of dietary advice on the diet of men with angina: the diet and angina randomized trial. *Journal of Human Nutrition and Dietetics* 2004;17:1–3.

Ness AR, Gallacher JE, Bennett PD, Gunnell DJ, Rogers PJ, Kessler D, et al. Advice to eat fish and mood: a randomised controlled trial in men with angina. *Nutritional Neuroscience* 2003;**6**(1):63–5.

DART fish Burr 1989 {published and unpublished data}

Burr ML, Fehily AM. Fatty fish and heart disease: a randomized controlled trial. *World Review of Nutrition and Dietetics* 1991;**66**:306–12.

Burr ML, Fehily AM. Fish and the heart [letter]. *Lancet* 1989;**ii**:1451-2.

* Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;**2**(8666):757–61. Burr ML, Fehily AM, Rogers S, Welsby E, King S, Sandham S. Diet and reinfarction trial (DART): design, recruitment, and compliance. *European Heart Journal* 1989;**10**(6): 558–67.

Burr ML, Holliday RM, Fehily AM, Whitehead PJ. Haematological prognostic indices after myocardial infarction: evidence from the diet and reinfarction trial (DART). European Heart Journal 1992;13(2):166–70. Burr ML, Sweetham PM, Fehily AM. Diet and reinfarction [letter]. European Heart Journal 1994;15(8):1152–3. Fehily AM, Vaughan-Williams E, Shiels K, Williams AH, Horner M, Bingham G, et al. Factors influencing compliance with dietary advice: the Diet and Reinfarction Trial (DART). Journal of Human Nutrition and Dietetics 1991;4:33–42.

Fehily AM, Vaughan-Williams E, Shiels K, Williams AH, Horner M, Bingham G, et al. The effect of dietary advice on nutrient intakes: evidence from the diet and reinfarction trial (DART). *Journal of Human Nutrition & Dietetics* 1989; 2:4735

Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction Trial (DART). *European Journal of Clinical Nutrition* 2002; **56**(6):512–8.

Ness AR, Whitley E, Burr ML, Elwood PC, Smith GD, Ebrahim S. The long-term effect of advice to eat more fish on blood pressure in men with coronary disease: results from the diet and reinfarction trial. *Journal of Human Hypertension* 1999;**13**(11):729–33.

Derosa 2016 {published and unpublished data}

Derosa G, Cicero AF, D'Angelo A, Borghi C, Maffioli P. Effects of n-3 PUFAs on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance. *BioFactors (Oxford, England)* 2016;42(3):316–22. PUBMED: 27040503]

Deslypere 1992 {published and unpublished data}

Blok WL, Deslypere JP, Demacker PN, Van der Ven-Jongekrijg J, Hectors MP, Van der Meer JW, et al. Proand anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. *European Journal of Clinical Investigation* 1997;**27**(12):1003–8. PUBMED: 9466128]

* Deslypere JP. Influence of supplementation with n-3 fatty acids on different coronary risk factors in men: a placebo controlled study. Verhandelingen - Koninklijke Vlaamse Academie voor Geneeskunde van Belgie 1992;**54**(3):189–216. PUBMED: 1413984]

Katan MB, Deslypere JP, Van Birgelen AP, Penders M, Zegwaard M. Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. *Journal of Lipid Research* 1997;**38**(10):2012–22. PUBMED: 93741241

DISAF - Harrison 2005 {published and unpublished data}

Harrison RA, Elton P. From pies to pilchards: dietary assistants increase consumption of oil rich fish. *Journal of Epidemiology and Community Health* 2000;**Suppl**:6.
Harrison RA, Elton PJ. Can an oil-rich fish diet improve treatment outcomes following cardioversion for atrial fibrillation? A randomised controlled trial. Study design and compliance [poster]. International Society for the Study of Fatty Acids and Lipids (ISSFAL); 2003; Montreal, Canada 2003

* Harrison RA, Elton PJ. Is there a role for long-chain omega3 or oil-rich fish in the treatment of atrial fibrillation?

. Medical Hypotheses 2005;64(1):59–63. PUBMED: 155336121

Harrison RA, Purnell P, Elton PJ. Using community-based dietary assistants to increase the intake of oil-rich fish among older people. *European Journal of Public Health* 2003;13 (Suppl 1):105.

DO Health {published data only}

NCT01745263. DO-HEALTH / vitamin D3 - omega3 - home exercise - healthy ageing and longevity trial. clinicaltrials.gov/ct2/show/NCT01745263 (first posted 10 December 2012).

DO IT 2006 {published and unpublished data}

Berstad P, Seljeflot I, Veierod MB, Hjerkinn EM, Arnesen H, Pedersen JI, et al. Supplementation with fish oil affects the association between very long-chain n-3 polyunsaturated fatty acids in serum non-esterified fatty acids and soluble vascular cell adhesion molecule-1. *Clinical Science* 2003; **105**(1):13–20.

Ellingsen I, Hjerkinn EM, Seljeflot I, Arnesen H, Tonstad S, Ellingsen I, et al. Consumption of fruit and berries is inversely associated with carotid atherosclerosis in elderly men. *British Journal of Nutrition* 2008;99(3):674-81 (Erratum in: British Journal of Nutrition 2008;99(3):697). Ellingsen I, Seljeflot I, Arnesen H, Tonstad S, et al. Vitamin C consumption is associated with less progression in carotid intima media thickness in elderly men: a 3-year intervention study. *Nutrition Metabolism & Cardiovascular Diseases* 2009;19(1):8–14.

Furenes EB, Seljeflot I, Solheim S, Hjerkinn EM, Arnesen H, Furenes EB, et al. Long-term influence of diet and/ or omega-3 fatty acids on matrix metalloproteinase-9 and pregnancy-associated plasma protein A in men at high risk of coronary heart disease. *Scandinavian Journal of Clinical & Laboratory Investigation* 2008;**68**(3):177–84.

* Hjerkinn EM, Abdelnoor M, Breivik L, Bergengen L, Ellingsen I, Seljeflot I, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. *European Journal of Cardiovascular Prevention & Rehabilitation* 2006;**13**(3):325–33.

Hjerkinn EM, Seljeflot I, Ellingsen I, Berstad P, Hjermann I, Sandvik L, et al. Influence of long-term intervention with dietary counselling, long-chain n-3 fatty acid supplements, or both on circulating markers of endothelial activation in men with long-standing hyperlipidemia. *American Journal of Clinical Nutrition* 2005;81(3):583–9.

Lindman AS, Pedersen JI, Hjerkinn EM, Arnesen H, Veierod MB, Ellingsen I, et al. The effects of long-term diet and omega-3 fatty acid supplementation on coagulation factor VII and serum phospholipids with special emphasis on the R353Q polymorphism of the FVII gene. *Thrombosis & Haemostasis* 2004;**91**(6):1097–104.

Troseid M, Arnesen H, Hjerkinn EM, Seljeflot I. Serum levels of interleukin-18 are reduced by diet and n-3 fatty acid intervention in elderly high-risk men. *Metabolism: Clinical & Experimental* 2009;**58**(11):1543–9.

Troseid M, Seljeflot I, Hjerkinn EM, Arnesen H. Interleukin-18 is a strong predictor of cardiovascular events in elderly men with the metabolic syndrome: synergistic effect of inflammation and hyperglycemia. *Diabetes Care* 2009;**32**(3):486–92.

DO IT - Einvik 2010 {published and unpublished data}

Berstad P, Seljeflot I, Veierod MB, Hjerkinn EM, Arnesen H, Pedersen JI. Supplementation with fish oil affects the association between very long-chain n-3 polyunsaturated fatty acids in serum non-esterified fatty acids and soluble vascular cell adhesion molecule-1. *Clinical Science* 2003; **105**(1):13–20.

Eid HM, Arnesen H, Hjerkinn EM, Lyberg T, Ellingsen I, Seljeflot I. Effect of diet and omega-3 fatty acid intervention on asymmetric dimethylarginine. *Nutrition & Metabolism* 2006;**3**:4.

Eid HMA, Arnesen H, Hjerkinn EM, Lyberg T, Ellingsen I, Seljeflot I. Effect of diet and omega-3 fatty acid intervention on asymmetric dimethylarginine. *Nutrition and Metabolism* 2006;**3**:1–10.

Einvik G, Ekeberg O, Lavik JG, Ellingsen I, Klemsdal TO, Hjerkinn EM. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. *Journal of Psychosomatic Research* 2010;**68**(6):567–72.

* Einvik G, Klemsdal TO, Sandvik L, Hjerkinn EM. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. European Journal of Cardiovascular Prevention & Rehabilitation 2010;17(5):588–92.

Ellingsen I, Hjerkinn EM, Arnesen H, Seljeflot I, Hjermann I, Tonstad S. Follow-up of diet and cardiovascular risk factors 20 years after cessation of intervention in the Oslo Diet and Antismoking study. *European Journal of Clinical Nutrition* 2006;**60**(3):378–85.

Furenes EB, Seljeflot I, Solheim S, Hjerkinn EM, Arnesen H, Furenes EB. Long-term influence of diet and/or

omega-3 fatty acids on matrix metalloproteinase-9 and pregnancy-associated plasma protein A in men at high risk of coronary heart disease. *Scandinavian Journal of Clinical and Laboratory Investigation* 2008;**68**(3):177–84.

Hjerkinn EM, Abdelnoor M, Breivik L, Bergengen L, Ellingsen L, Selieflot L, et al., Effect of diet or very long

Ellingsen I, Seljeflot I, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. European Journal of Cardiovascular Prevention & Rehabilitation 2006;13(3):325–33.

Hjerkinn EM, Seljeflot I, Ellingsen I, Berstad P, Hjermann I, Sandvik L, et al. Influence of long-term intervention with dietary counseling, long-chain n-3 fatty acid supplements, or both on circulating markers of endothelial activation in men with long-standing hyperlipidemia. *American Journal of Clinical Nutrition* 2005;81(3):583–9.

Lindman AS, Pedersen JI, Hjerkinn EM, Arnesen H, Veierod MB, Ellingsen I, et al. The effects of long-term diet and omega-3 fatty acid supplementation on coagulation factor VII and serum phospholipids with special emphasis on the R353Q polymorphism of the FVII gene. *Thrombosis & Haemostasis* 2004;**91**(6):1097–104.

Troseid M, Arnesen H, Hjerkinn EM, Seljeflot I. Serum levels of interleukin-18 are reduced by diet and n-3 fatty acid intervention in elderly high-risk men. *Metabolism: Clinical and Experimental* 2009;**58**(11):1543–9.

Troseid M, Seljeflot I, Weiss TW, Klemsdal TO, Hjerkinn EM, Arnesen H. Arterial stiffness is independently associated with interleukin-18 and components of the metabolic syndrome. *Atherosclerosis* 2010;**209**(2):337–9.

EPE-A study 2014 {published and unpublished data}

Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology* 2014;**147**(2):377–84.e1. PUBMED: 24818764]

Erdogan 2007 {published data only}

* Erdogan A, Bayer M, Kollath D, Greiss H, Voss R, Neumann T, et al. Omega AF study: polyunsaturated fatty acids (PUFA) for prevention of atrial fibrillation relapse after successful external cardioversion. *Heart Rhythm* 2007; 4(5):S185–6.

Heidt MC, Vician M, Stracke SKH, Stadlbauer T, Grebe MT, Boening A, et al. Beneficial effects of intravenously administered n-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thoracic and Cardiovascular Surgeon* 2009;57:276–80. DOI: 10.1055/s-0029-1185301 Mariani J, Doval HC, Nul D, Varini S, Grancelli H, Ferrante D, et al. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. *Journal of the American Heart Association* 2013;2(1):e005033.

Finnish Mental Hosp 1972 {published data only}

* Miettinen M, Turpeinen O, Karvonen MJ, Elosuo R, Paavilainen E. Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes: a twelve-year clinical trial in men and women. *Lancet* 1972;**2** (782):835–8.

Miettinen M, Turpeinen O, Karvonen MJ, Pekkarinen M, Paavilainen E, Elosuo R. Dietary prevention of coronary heart disease in women: the Finnish mental hospital study. *International Journal of Epidemiology* 1983;**12**(1):17–25. Turpeinen O, Miettinen M, Karvonen M, Roine P, Pekkarinen M, Lehtosuo EJ, et al. Dietary prevention of coronary heart disease: long-term experiment. I. Observations on male subjects. *American Journal of Clinical Nutrition* 1968;**21**(4):255–76.

FLAX-PAD 2013 {published data only}

Caligiuri SP, Aukema HM, Ravandi A, Guzman R, Dibrov E, Pierce GN. Flaxseed consumption reduces blood pressure in patients with hypertension by altering circulating oxylipins via an alpha-linolenic acid-induced inhibition of soluble epoxide hydrolase. *Hypertension* 2014;**64**(1):53–9. PUBMED: 24777981]

Caligiuri SP, Rodriguez-Leyva D, Aukema HM, Ravandi A, Weighell W, Guzman R, et al. Dietary flaxseed reduces central aortic blood pressure without cardiac involvement but through changes in plasma oxylipins. *Hypertension* 2016;**68**(4):1031–8. PUBMED: 27528063]

* Edel A, Rodriguez-Leyva D, Weighell W, La Vallee R, Aliani M, Guzman R, et al. Flaxseed lignan metabolites elicit antihypertensive effects in pad patients in the flax-pad trial. Annals of Nutrition and Metabolism 2013;63:1339. Edel AL, Rodriguez-Leyva D, Maddaford TG, Caligiuri SP, Austria JA, Weighell W, et al. Dietary flaxseed independently lowers circulating cholesterol and lowers it beyond the effects of cholesterol-lowering medications alone in patients with peripheral artery disease. Journal of Nutrition 2015;145(4):749-57. PUBMED: 25694068] Leyva DR, Zahradka P, Ramjiawan B, Guzman R, Aliani M, Pierce GN. The effect of dietary flaxseed on improving symptoms of cardiovascular disease in patients with peripheral artery disease: rationale and design of the FLAX-PAD randomized controlled trial. Contemporary Clinical Trials 2011;32(5):724-30. PUBMED: 21616170] Pierce GN, Edel AL, LaVallee R, Caligiuri S, Aukema H, Ravandi A, et al. The use of dietary flasseed to promote cardiovascular health. Acta Physiologica 2014;211:15. Pierce GN, Rodriguez-Leyva D, Edel A, Guzman R, Aliani M. The clinical use of flaxseed as a powerful nutritional intervention to treat cardiovascular disease. Cardiology

Rodriguez-Leyva D, Weighell W, Edel AL, LaVallee R, Dibrov E, Pinneker R, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. *Hypertension* 2013;**62**(6):1081–9. PUBMED: 24126178]

FORWARD 2013 {published and unpublished data}

(Switzerland) 2013;126:201.

* Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (randomized trial to assess efficacy of PUFA for the maintenance of sinus rhythm in persistent

atrial fibrillation) trial. *Journal of the American College of Cardiology* 2013;**61**(4):463–8. PUBMED: 23265344] Macchia A, Varini S, Grancelli H, Nul D, Laffaye N, Ferrante D, et al. The rationale and design of the FORomegaARD trial: a randomized, double-blind, placebo-controlled, independent study to test the efficacy of n-3 PUFA for the maintenance of normal sinus rhythm in patients with previous atrial fibrillation. *American Heart Journal* 2009;**157**(3):423–7. PUBMED: 19249410]

FOSTAR 2016 {published and unpublished data}

Chen JS, Hill CL, Lester S, Ruediger CD, Battersby R, Jones G, et al. Supplementation with omega-3 fish oil has no effect on bone mineral density in adults with knee osteoarthritis: a 2-year randomized controlled trial. *Osteoporosis International* 2016;**27**(5):1897–905. PUBMED: 26694596]

Hill C, Lester SE, Jones G. Response to 'Low-dose versus high-dose fish oil for pain reduction and function improvement in patients with knee osteoarthritis' by Chen et al. Annals of the Rheumatic Diseases 2016; Vol. 75, issue 1:e8. PUBMED: 26662278]

* Hill CL, March LM, Aitken D, Lester SE, Battersby R, Hynes K, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. *Annals of the Rheumatic Diseases* 2016;75(1):23–9. PUBMED: 26353789]

Franzen 1993 {published and unpublished data}

Franzen D. Unknown. *Catheterization and Cardiovascular Diagnosis* 1993;**28**:301–10.

* Franzen D, Geisel J, Hopp HW, Oette K, Hilger HH. Long-term effects of low dosage fish oil on serum lipids and lipoproteins [Langzeiteffekte von niedrigdosiertem fischol auf serumlipide und lipoproteine]. *Medizinische Klinik* 1993;88(3):134–8.

Gill 2012 {published data only}

Gill EA, Chen MA, Paramsothy P, Fish B, Isquith D, Thirumalai A, et al. Abstract 12697: Omega-3 fatty acids effects on carotid IMT in metabolic syndrome. *Circulation* 2014;**130**:A1269.

* Gill EA, Chen MA, Thirumalai A, Fish B, Paramsothy P. Omega-3 fatty acids improve dyslipidemia but not inflammatory markers in metabolic syndrome. *Journal of Clinical Lipidology* 2012;**6**:278–9.

GISSI-HF 2008 {published data only}

Aleksova A, Masson S, Maggioni AP, Lucci D, Fabbri G, Beretta L, et al. N-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. *European Journal of Heart Failure* 2013;**15**(11): 1289–95.

Canepa M, Temporelli PL, Rossi A, Gonzini L, Nicolosi GL, Staszewsky L, et al. Prevalence and prognostic impact of chronic obstructive pulmonary disease in patients with chronic heart failure. Data from the GISSI-Heart Failure trial. *European Journal of Heart Failure* 2016;**18**:442–3. Cowie MR, Cure S, Bianic F, McGuire A, Goodall G, Tavazzi L. Cost-effectiveness of highly purified omega-3 polyunsaturated fatty acid ethyl esters in the treatment of

chronic heart failure: results of Markov modelling in a UK setting. *European Journal of Heart Failure* 2011;**13**(6): 681–9. DOI: 10.1093/eurjhf/hfr023

Finzi A, Barlera S, Serra DM, Rossi MG, Ruggeri A, Mezzani A, et al. Antiarrhythmic effects of n-3 PUFA in patients with heart failure and an implantable cardioverter defibrillator in the GISSI-HF trial. *European Heart Journal* 2009;30:279.

Finzi AA, Latini R, Barlera S, Rossi MG, Ruggeri A, Mezzani A, et al. Effects of n-3 polyunsaturated fatty acids on malignant ventricular arrhythmias in patients with chronic heart failure and implantable cardioverter-defibrillators: a substudy of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial. *American Heart Journal* 2011;**161**(2): 338–43. DOI: 10.1016/j.ahj.2010.10.032

Ghio S, Scelsi L, Latini R, Masson S, Eleuteri E, Palvarini M, et al. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. *European Journal of Heart Failure* 2010;**12**(12):1345–53.

La Rovere MT, Barlera S, Staszewsky L, Mezzani A, Midi P, Marchioli R, et al. Effect of n-3PUFA on heart rate variability. Data from the GISSI-HF holter substudy. *Circulation* 2011;**124**(21 SUPPL 1):14829.

La Rovere MT, Pinna GD, Maestri R, Barlera S, Bernardinangeli M, Veniani M, et al. Autonomic markers and cardiovascular and arrhythmic events in heart failure patients: still a place in prognostication? Data from the GISSI-HF trial. *European Journal of Heart Failure* 2012;14 (12):1410–9.

La Rovere MT, Staszewsky L, Barlera S, Maestri R, Mezzani A, Midi P, et al. N-3PUFA and holter-derived autonomic variables in patients with heart failure: data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) Holter substudy. Heart Rhythm 2013;10(2):226–32.

Latini R, Masson S, Tacconi M, Bernasconi R, Dragani L, Milani V, et al. Circulating levels of n-3 polyunsaturated fatty acids in patients with chronic heart failure. Data from the GISSI-HF trial. European Heart Journal 2011;32:919. Maggioni AP, Fabbri G, Lucci D, Marchioli R, Franzosi MG, Latini R, et al. Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial. Eupropean Heart Journal 2009;30(19):232736. Marchioli R, Aldegheri MP, Borghese L, Franzosi MG, Latini R, Marfisi RM, et al. Time course analysis of the effect of n-3 PUFA on fatal and non fatal arrhythmias in heart failure: secondary results of the GISSI-HF trial. European Heart Journal 2009;30:165.

Marchioli R, Cucchi G, Gualco A, Franzosi MG, Levantesi G, Maggioni AP, et al. Time course analysis of the effect of n-3 PUFA on fatal and non fatal heart failure: Secondary results of the GISSI-HF trial. *European Heart Journal* 2009; **30**,632

Marchioli R, Franzosi MG, Latini R, Maggioni AP, Marfisi RM, Minneci C, et al. Prognostic ability of a Mediterranean

dietary score in heart failure: preliminary analysis of the GISSI-Heart failure trial. *European Heart Journal* 2009;**30**: 1026

Marchioli R, Franzosi MG, Latini R, Maggioni AP, Marfisi RM, Nicolosi GL, et al. Effect of n-3 PUFA in heart failure patients with different dietary habits: preliminary results of the GISSI-heart failure trial. *European Heart Journal* 2009; **30**:426

Marchioli R, Franzosi MG, Levantesi G, Marfisi RM, Maggioni AP, Nicolosi GL, et al. Effect of n-3 PUFA according to fish intake: preliminary results of GISSI-Heart Failure. *European Heart Journal* 2009;**30**:707.

Marchioli R, Levantesi G, Silletta MG, Barlera S, Bernardinangeli M, Carbonieri E, et al. Effect of n-3 polyunsaturated fatty acids and rosuvastatin in patients with heart failure: results of the GISSI-HF trial. *Expert Review of Cardiovascular Therapy* 2009;7(7):735–48.

Masson S, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, et al. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. *Circulation: Heart Failure* 2010;3(1):65–72.

Masson S, Marchioli R, Mozaffarian D, Bernasconi R, Milani V, Dragani L, et al. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure trial: relation with fish intake, circulating biomarkers, and mortality. *American Heart Journal* 2013;**165**(2):208–15. Røysland R, Masson S, Omland T, Milani V, Bjerre M, Flyvbjerg A, et al. Prognostic value of osteoprotegerin in chronic heart failure: the GISSI-HF trial. *American Heart Journal* 2010;**160**(2):286–93. DOI: 10.1016/j.ahj.2010.05.015

* Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372(9645):1223–30. DOI: 10.1016/S01406736(08)61239-8

Tavazzi L, Tognoni G, Franzosi MG, Latini R, Maggioni AP, Marchioli R, et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *European Journal of Heart Failure* 2004;6(5):635–41. DOI: 10.1016/j.ejheart.2004.03.001

GISSI-P 1999 {published data only}

Franzosi MG, Brunetti M, Marchioli R, Marfisi RM, Tognoni G, Valagussa F, et al. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione trial. *Pharmacoeconomics* 2001;**19**(4):411–20.

* GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;**354**:447–55.

Marchioli R. Treatment with n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-

Prevenzione trial. European Heart Journal Supplements 2001;3(Supplement D):D85–D97.

Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio DDMR, Franzosi MG, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 2002;**105**:1897–903.

Marchioli R, Di Pasquale A. The biochemical, pharmacological and epidemiological reference picture of the GISSI-Prevention. *Giornale Italiano di Cardiologia* 1993;**23**(9):933–64.

Marchioli R, Valagussa F. The results of the GISSI-Prevenzione trial in the general framework of secondary prevention. *European Heart Journal* 2000;**21**(12):949–52.

JELIS 2007 {published and unpublished data}

Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *The European Journal of Heart Failure* 2006;**8**(1):105–10. DOI: 10.1016/j.ejheart.2005.12.003

Ishikawa Y, Yokoyama M, Saito Y, Matsuzaki M, Origasa H, Oikawa S, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. *Circulation Journal* 2010;74(7):1451–7. DOI: 10.1253/circj.CJ-09-0520

Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Secondary prevention analysis from JELIS. *Circulation Journal* 2009;73(7):1283–90.

Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2009;**206** (2):535–9. DOI: 10.1016/j.atherosclerosis.2009.03.029 Origasa H, Yokoyama M, Matsuzaki M, Saito Y, Matsuzawa Y, JELIS Investigators. Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia. *Circulation Journal* 2010;74(3): 510–7. DOI: 10.1253/circj.CJ-09-0746

Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2008;**200**(1):135–40. DOI: 10.1016/j.atherosclerosis.2008.06.003

Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. *Stroke* 2008;**39**(8):2052–8. DOI: 10.1161/STROKEAHA.107.509455

Yamanouchi D, Komori K. Eicosapentaenoic acid as the

gold standard for patients with peripheral artery disease? Subanalysis of the JELIS trial. *Circulation Journal* 2010;74 (7):1298–9. DOI: 10.1253/circj.CJ-10-0449

* Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;**369**(9567):1090–8.

Yokoyama M, Origasa H, for the JELIS Investigators. Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolaemia: rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). *American Heart Journal* 2003; **146**:613–20.

Lorenz-Meyer 1996 {published and unpublished data}

Lorenz-Meyer H, Bauer P, Nicolay C, Schulz B, Purrmann J, Fleig WE, et al. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Study Group Members (German Crohn's Disease Study Group). Scandinavian Journal of Gastroenterology 1996;31(8): 778–85.

Mansel 1990 {published data only}

* Mansel RE, Gateley CA, Harrison BJ, Melhuish J, Sheridan W, Pye JK, et al. Effects and tolerability of n-6 essential fatty acid supplementation in patients with recurrent breast cysts: a randomized double-blind placebocontrolled trial. *Journal of Nutritional Medicine* 1990;**1**(3):

Mansel RE, Harrison BJ, Melhuish J, Sheridan W, Pye JK, Pritchard G, et al. A randomized trial of dietary intervention with essential fatty acids in patients with categorized cysts. *Annals of the New York Academy of Sciences* 1990;**586**:288–94.

Mansel RE, Pye JK, Hughes LE. Effects of essential fatty acids on cyclical mastalgia and noncyclical breat disorders. In: Horrobin DE editor(s). *Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine*. 1st Edition. New York: Wiley-Liss, 1990:557–66. ISBN 0–471–SAh93–4]

MAPT 2017 {published data only}

* Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebocontrolled trial. *Lancet Neurology* 2017;16:377–89. DOI: 10.1016/S1474-4422(17)30040-6

Carrie I, Van Kan GA, Gillette-Guyonnet S, Andrieu S, Dartigues JF, Touchon J, et al. Recruitment strategies for preventive trials. The MAPT study (MultiDomain Alzheimer Preventive Trial). *Journal of Nutrition, Health & Aging* 2012;**16**(4):355–9.

Delrieu J, Andrieu S, Pahor M, Cantet C, Cesari M, Ousset PJ, et al. Neuropsychological profile of "cognitive frailty" subjects in MAPT study. *Journal of Prevention of Alzheimer's*

Disease 2016;3(3):151–9. DOI: 10.14283/jpad.2016.94 Delrieu J, Payoux P, Hitzel A, Peiffer S, Abellan Van Kan G, Gillette S, et al. Multidomain Alzheimer's disease preventive trial: Florbetapir ancillary study. Alzheimer's & Dementia 2011:1:S419.

Fougere B, Barreto PD, Goisser S, Soriano G, Guyonnet S, Andrieu S, et al. Red blood cell membrane omega-3 fatty acid levels and physical performance: cross-sectional data from the MAPT study. Clinical Nutrition 2017;pii(S0261-5614(17)30128-0):1-4. DOI: 10.1016/j.clnu.2017.04.005 Gillette S. The multidomain Alzheimer preventive trial (MAPT): a new approach for the prevention of Alzheimer's disease. Alzheimer's & Dementia 2009;5(4):145. Gillette-Guyonnet S, Andrieu S, Dantoine T, Dartigues JF, Touchon J, Vellas B, et al. Commentary on "A roadmap for the prevention of dementia II. Leon Thal Symposium 2008." The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. Alzheimer's & Dementia 2009;5(2):114-21. Gillette-Guyonnet S, Vellas B, Andrieu S, Dupuy C, Carrié I. MAPT study: a 3-year randomized trial of omega 3 and/ or multidomain intervention for the prevention of cognitive decline in frail elderly subjects-rationale, design and baseline data. Alzheimer's & Dementia 2011;1:S97-8. Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J,

Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartigues JF, et al. MAPT study: a multidomain approach for preventing ALzheimer's disease: design and baseline data. *Journal of Prevention of Alzheimers Disease* 2014;1(1):13–22.

Vellas B, Carrie I, Guyonnet S, Touchon J, Dantoine T, Dartigues JF, et al. MAPT (multi-domain Alzheimer's prevention trial): results at 36 months. *Alzheimer's & Dementia* 2015;**1**:331.

Vellas B, Touchon J, Weiner M. MAPT (multidomain Alzheimer preventive trial) imaging (MRI, FDG-PET, amyloid-PET) data. *Journal of Nutrition, Health and Aging* 2012;**16** (9):812–5.

MARGARIN Bemelmans 2002 {published data only (unpublished sought but not used)}

Bemelmans WJ, Broer J, De Vries JH, Hulshof KF, May JF, Meyboom-De Jong B. Impact of Mediterranean diet education versus posted leaflet on dietary habits and serum cholesterol in a high risk population for cardiovascular disease. *Public Health Nutrition* 2000;**3**(3):273–83.

* Bemelmans WJ, Broer J, Feskens EJ, Smit AJ, Muskiet AJ, Lefrandt JD, et al. Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean alpha-linolenic enriched Groningen dietary intervention (MARGARIN) study. *American Journal of Clinical Nutrition* 2002;**75**:221–7.

Bemelmans WJ, Lefrandt JD, Feskens EJ, Broer J, Tervaert JW, May JF, et al. Change in saturated fat intake is associated with progression of carotid and femoral intimamedia thickness, and with levels of soluble intercellular adhesion molecule-1. *Atherosclerosis* 2002;**163**(1):113–20. Bemelmans WJ, Lefrandt JD, Feskens EJ, Van Haelst

PL, Broer J, Meyboom-de Jong B, et al. Increased alphalinolenic acid intake lowers C-reactive protein, but has no effect on markers of atherosclerosis. *European Journal of Clinical Nutrition* 2004;**58**(7):1083–9.

Bemelmans WJ, Muskiet FA, Feskens EJ, De Vries JH, Broer J, May JF, et al. Associations of alpha-linolenic acid and linoleic acid with risk factors for coronary heart disease. *European Journal of Clinical Nutrition* 2000;**54**(12):865–71. Siero FW, Broer J, Bemelmans WJ, Meyboom-de Jong BM. Impact of group nutrition education and surplus value of Prochaska based stage-matched information on health-related cognitions and on Mediterranean nutrition behaviour. *Health Education Research* 2000;**15**(5):635–47.

MENU - Rock 2016 {published data only}

Le T, Flatt SW, Natarajan L, Pakiz B, Quintana EL, Heath DD, et al. Effects of diet composition and insulin resistance status on plasma lipid levels in a weight loss intervention in women. *Journal of the American Heart Association* 2016;**5** (1):e002771. DOI: 10.1161/JAHA.115.002771

* Rock CL, Flatt SW, Pakiz B, Quintana EL, Heath DD, Rana BK, et al. Effects of diet composition on weight loss, metabolic factors and biomarkers in a 1-year weight loss intervention in obese women examined by baseline insulin resistance status. *Metabolism* 2016;**65**(11):1605–13. DOI: 10.1016/j.metabol.2016.07.008

Michalsen 2006 {published data only}

Michalsen A, Lehmann N, Pithan C, Knoblauch NT, Moebus S, Kannenberg F, et al. Mediterranean diet has no effect on markers of inflammation and metabolic risk factors in patients with coronary artery disease. *European Journal of Clinical Nutrition* 2006;**60**(4):478–85.

Middleton 2002 {published data only}

Middleton SJ, Naylor S, Woolner J, Hunter JO. A double-blind, randomized, placebo-controlled trial of essential fatty acid supplementation in the maintenance of remission of ulcerative colitis. *Alimentary Pharmacology & Therapeutics* 2002;**16**(6):1131–5. PUBMED: 12030955]

Minnesota Coronary 1989 {published data only}

Brewer ER, Ashman PL, Kuba K. The Minnesota Coronary Survey: composition of diets, adherence and serum lipid response. Circulation 1975;51 and 52(Suppl II):269. Dawson EA, Gatewood LC. The Minnesota Coronary Survey: methodology and characteristics of the population. Circulation 1975;51 and 52(Suppl II):271. * Frantz ID Jr, Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, et al. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. Arteriosclerosis 1989;9(1):129-35. Frantz ID, Dawson EA, Kuba K, et al. The Minnesota Coronary Survey: effect of diet on cardiovascular events and deaths. Circulation 1975;51 and 52(Suppl II):4. Ramsden CE, Zamora D, Majchrzak-Hong S, Faurot KR, Broste SK, Frantz RP, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). BMJ 2016; 353:i1246.

Moy 2001 {published and unpublished data}

Moy TF, Yanek LR, Raqueno JV, Bezirdjian PJ, Blumenthal RS, Wilder LB, et al. Dietary counseling for high blood cholesterol in families at risk of coronary disease. *Preventive Cardiology* 2001;4(4):158–64.

NAT2 2015 {published data only}

Merle BM, Benlian P, Puche N, Bassols A, Delcourt C, Souied EH. Circulating omega-3 fatty acids and neovascular age-related macular degeneration. *Investigative Ophthalmology & Visual Science* 2014;**55**(3):2010–9. PUBMED: 24557349]

* Merle BM, Richard F, Benlian P, Puche N, Delcourt C, Souied EH. CFH Y402H and ARMS2 A69S polymorphisms and oral supplementation with docosahexaenoic acid in neovascular age-related macular degeneration patients: the NAT2 study. *PloS One* 2015;**10**(7):e0130816. PUBMED: 26132079]

Querques G, Merle BM, Pumariega NM, Benlian P, Delcourt C, Zourdani A, et al. Dynamic drusen remodelling in participants of the Nutritional AMD Treatment-2 (NAT-2) randomized trial. *PloS One* 2016;**11**(2):e0149219. PUBMED: 26901353]

Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. *Ophthalmology* 2013;**120**(8):1619–31. PUBMED: 23395546]

Norouzi 2014 {published data only}

* Norouzi Javidan A, Sabour H, Latifi S, Abrishamkar M, Soltani Z, Shidfar F, et al. Does consumption of polyunsaturated fatty acids influence on neurorehabilitation in traumatic spinal cord-injured individuals? A double-blinded clinical trial. *Spinal Cord* 2014;**52**(5):378–82. PUBMED: 24637568

Sabour H, Norouzi Javidan A, Latifi S, Shidfar F, Heshmat R, Emami Razavi SH, et al. Omega-3 fatty acids' effect on leptin and adiponectin concentrations in patients with spinal cord injury: a double-blinded randomized clinical trial. *Journal of Spinal Cord Medicine* 2015;38(5):599–606. PUBMED: 25096818]

Norwegian - Natvig 1968 {published data only}

Natvig H. The effect of unsaturated fatty acids on the incidence of coronary infarction, etc. *Tidsskrift for Den Norske Laegeforening* 1967;**87**(11):1033–41.

* Natvig H, Borchgrevink CF, Dedichen J, Owren PA, Schiotz EH, Westlund K. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. Scandinavian Journal of Clinical & Laboratory Investigation - Supplement 1968;105:1–20.

NutriStroke 2009 {published data only}

Garbagnati F, Cairella G, De Martino A, Multari M, Scognamiglio U, Venturiero V, et al. Is antioxidant and n-3 supplementation able to improve functional status in post-stroke patients? Results from the Nutristroke Trial. *Cerebrovascular Diseases (Basel, Switzerland)* 2009;**27**(4): 375–83. DOI: 10.1159/000207441

OFAMI - Nilsen 2001 {published and unpublished data}

Aarsetoy H, Brugger-Andersen T, Hetland O, Grundt H, Nilsen DW. Long term influence of regular intake of high dose n-3 fatty acids on CD40-ligand, pregnancy-associated plasma protein A and matrix metalloproteinase-9 following acute myocardial infarction. *Thrombosis & Haemostasis* 2006;95(2):329–36.

Grundt H, Hetland O, Nilsen DW. Changes in tissue factor and activated factor XII following an acute myocardial infarction were uninfluenced by high doses of n-3 polyunsaturated fatty acids. *Thrombosis & Haemostasis* 2003;**89**(4):752–9.

Grundt H, Nilsen DW, Hetland O, Mansoor MA. Clinical outcome and atherothrombogenic risk profile after prolonged wash-out following long-term treatment with high doses of n-3 PUFAs in patients with an acute myocardial infarction. *Clinical Nutrition* 2004;23(4): 491–500.

Grundt H, Nilsen DW, Mansoor MA, Hetland O, Nordoy A. Reduction in homocysteine by n-3 polyunsaturated fatty acids after 1 year in a randomised double-blind study following an acute myocardial infarction: no effect on endothelial adhesion properties. *Pathophysiology of Haemostasis & Thrombosis* 2003;33(2):88–95.

Grundt H, Nilsen DW, Mansoor MA, Nordoy A. Increased lipid peroxidation during long-term intervention with high doses of n-3 fatty acids (PUFAs) following an acute myocardial infarction. *European Journal of Clinical Nutrition* 2003;57(6):793–800.

Naesgaard PA, Grundt H, Brede C, Nilsen DW. The effect on vitamin D levels of long-term high-dose treatment with a concentrated omega-3 compound (Omacor/lovaza) in patients hospitalized with a myocardial infarction. Circulation 2014;**130**(Suppl 2):A17245.

* Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *American Journal of Clinical Nutrition* 2001;**74**(1):50–6. Poenitz V, Grundt H, Bottazzi B, Cuccovillo I, Mantovani A, Nilsen DW. Pentraxin 3 is uninfluenced by high doses of concentrated omega-3 fatty acids administered for 12 months following an acute myocardial infarction. *Circulation* 2012;**126**(21 Suppl 1):A13464.

OMEGA 2014 {published and unpublished data}

* Rauch B, Riemer T, Schwaab B, Schneider S, Diller F, Gohlke H, et al. Short-term comprehensive cardiac rehabilitation after AMI is associated with reduced 1-year mortality: results from the OMEGA study. *European Journal of Preventive Cardiology* 2014;**21**(9):1060–9.

Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation* 2010;**122**(21):2152–9. DOI: 10.1161/CIRCULATIONAHA.110.948562

Rauch B, Schiele R, Schneider S, Gohlke H, Diller F,

Gottwik M, et al. Highly purified omega-3 fatty acids for secondary prevention of sudden cardiac death after myocardial infarction-aims and methods of the OMEGA-study. Cardiovascular Drugs and Therapy / Sponsored by the International Society of Cardiovascular Pharmacotherapy 2006;20(5):365–75. DOI: 10.1007/s10557-006-0495-6

OPAL - Dangour 2010 {published and unpublished data}

* Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *American Journal of Clinical Nutrition 2010;91(6):1725–32. Dangour AD, Allen E, Elbourne D, Fletcher A, Richards M, Uauy R. Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. *Journal of Nutrition, Health & Aging 2009;13(3):198–202. Dangour AD, Allen E, Elbourne D, Fletcher AE, Neveu MM, Uauy R, et al. N-3 fatty acids and retinal function. *Ophthalmology 2013;120(3):643. DOI: http://dx.doi.org/10.1016/j.ophtha.2012.09.043

Dangour AD, Clemens F, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. *Nutrition Journal* 2006;5: 20.

ORIGIN 2012 {published data only}

Bordeleau L, Yakubovich N, Dagenais G, Rosenstock J, Ryden LE, Spinas G, et al. Cancer outcomes in patients with dysglycemia on basal insulin: results of the ORIGIN trial. *Diabetes* 2013;**62**:A72.

Bordeleau L, Yakubovich N, Dagenais GR, Rosenstock J, Probstfield J, Chang Yu P, et al. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. *Diabetes Care* 2014;**37**(5): 1360–6.

Lonn EM, Bosch J, Diaz R, Lopez-Jaramillo P, Ramachandran A, Hancu N, et al. Effect of insulin glargine and n-3FA on carotid intima-media thickness in people with dysglycemia at high risk for cardiovascular events: the glucose reduction and atherosclerosis continuing evaluation study (ORIGIN-GRACE). *Diabetes Care* 2013;**36**(9): 2466–74.

Maggioni AP, Fabbri G, Bosch J, Dyal L, Ryden LE, Gerstein HC, et al. Effects of n-3 fatty acids on long-term outcomes of high risk patients with type 2 diabetes mellitus or IGF/IGT with a recent myocardial infarction. *European Heart Journal* 2013;34:352.

* Origin Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, et al. N-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *New England Journal of Medicine* 2012;**367**(4):309–18. Origin Trial Investigators, Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design, and baseline characteristics for a large international trial of cardiovascular

disease prevention in people with dysglycemia: the ORIGIN trial (Outcome Reduction with an Initial Glargine Intervention). *American Heart Journal* 2008;**155**(1):26-32, 32

Origin Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *New England Journal of Medicine* 2012;**367**(4):319–28. Punthakee Z, Gerstein HC, Bosch J, Tyrwhitt J, Jung H, Lee SF, et al. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). *Diabetes Care* 2016;**39**(5):709–16.

Oslo Diet-Heart 1966 {published and unpublished data}

Leren P. Prevention of coronary heart disease, some results from the Oslo secondary and primary intervention studies. *Journal of the American College of Nutrition* 1989;**8**:407–10. Leren P. The Oslo diet-heart study. Eleven year report. *Circulation* 1970;**42**:935–42.

Leren P. The effect of a cholesterol lowering diet in male survivors of myocardial infarction (a controlled clinical trial) [Virkningen av cholesterolsenkende diett hos menn som har gjennomgatt hjerteinfarkt. Et kontrollert klinisk fors/ok]. *Nordisk Medicin* 1967;77(21):658–61.

* Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Medica Scandinavica. Supplementum* 1966;466:1–92.

Leren P. The effect of plasma-cholesterol-lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Bulletin of the New York Academy of Medicine* 1968;44:1012–20.

Oxford Retinopathy 1978 {published and unpublished data}

Coppack SW, Doll HA, Pim B, Hockaday TDR. Intravenous glucose tolerance and mortality in non-insulindependant diabetes mellitus. *Quarterly Journal of Medicine* 1990;**75**:451–60.

Hillson RM, Hockaday TDR, Mann JI, Newton DJ. Hyperinsulinaemia is associated with development of ECG abnormalities in diabetics. *Diabetes Research* 1984;1:143–9.

* Hockaday TD, Hockaday JM, Mann JI, Turner RC. Prospective comparison of modified fat-high-carbohydrate with standard low-carbohydrate dietary advice in the treatment of diabetes: one year follow-up study. *British Journal of Nutrition* 1978;39(2):357–62.

Howard-Williams J, Patel P, Jelfs R, Carter RD, Awdry P, Bron A, et al. Polyunsaturated fatty acids and diabetic retinopathy. *British Journal of Ophthalmology* 1985;69(1):

Lopez-Espinoza I, Howard WJ, Mann JI, Carter RD, Hockaday TD. Fatty acid composition of platelet phospholipids in non-insulin-dependent diabetics randomized for dietary advice. *British Journal of Nutrition* 1984;**52**(1):41–7.

Özaydin 2011 {published data only}

Özaydin M, Erdoğ an D, Tayyar S, Uysal BA, Doğ an A, Içli A, et al. N-3 polyunsaturated fatty acids

administration does not reduce the recurrence rates of atrial fibrillation and inflammation after electrical cardioversion: a prospective randomized study. *Anadolu Kardiyoloji Dergisi* 2011;**11**(4):305–9. DOI: 10.5152/akd.2011.080

POUNDS Lost Sacks 2009 {published and unpublished data}

* Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *New England Journal of Medicine* 2009;**360**(9):859–73. de Souza RJ, Bray GA, Carey VJ, Hall KD, LeBoff MS, Loria CM, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. *American Journal of Clinical Nutrition* 2012;**95** (3):614–25. DOI: 10.3945/ajcn.111.026328

Ramirez-Ramirez 2013 {published data only}

* Ramirez-Ramirez V, Macias-Islas MA, Ortiz GG, Pacheco-Moises F, Torres-Sanchez ED, Sorto-Gomez TE, et al. Efficacy of fish oil on serum of TNF α , IL-1 β , and IL-6 oxidative stress markers in multiple sclerosis treated with interferon beta-1b. *Oxidative Medicine and Cellular Longevity* 2013;**2013**:709493. DOI: 10.1155/2013/709493

Sorto-Gomez TE, Ortiz GG, Pacheco-Moises FP, Torres-Sanchez ED, Ramirez-Ramirez V, Macias-Islas MA, et al. Effect of fish oil on glutathione redox system in multiple sclerosis. *American Journal of Neurodegenerative Disease* 2016;**5**(2):145–51.

Reed 2014 {published and unpublished data}

Olendzki BC, Leung K, Van Buskirk S, Reed G, Zurier RB. Treatment of rheumatoid arthritis with marine and botanical oils: influence on serum lipids. *Evidence-Based Complementary & Alternative Medicine: eCAM* 2011;**2011**: 827286.

* Reed GW, Leung K, Rossetti RG, Vanbuskirk S, Sharp JT, Zurier RB. Treatment of rheumatoid arthritis with marine and botanical oils: an 18-month, randomized, and double-blind trial. Evidence-Based Complementary & Alternative Medicine: eCAM 2014;2014:857456.

Risk and Prevention {published and unpublished data}

Rischio and Prevenzione Investigators. Efficacy of n-3 polyunsaturated fatty acids and feasibility of optimizing preventive strategies in patients at high cardiovascular risk: rationale, design and baseline characteristics of the Rischio and Prevenzione study, a large randomised trial in general practice. *Trials* 2010;**11**(1):68. DOI: 10.1186/1745-6215-11-68

* Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, et al. N-3 fatty acids in patients with multiple cardiovascular risk factors. *New England Journal of Medicine* 2013;**368**(19):1800–8.

Visentin G, Risk & Prevention Study Group. Towards evidence-based practice via practice-based evidence: the Italian experience. *Family Practice* 2008;**25 Suppl** 1:i71–4.

Sandhu 2016 {published data only}

* Sandhu N, Schetter SE, Liao J, Hartman TJ, Richie JP, McGinley J, et al. Influence of obesity on breast

density reduction by omega-3 fatty acids: evidence from a randomized clinical trial. *Cancer Prevention Research (Philadelphia, Pa.)* 2016;**9**(4):275–82. PUBMED: 26714774]

Signori C, DuBrock C, Richie JP, Prokopczyk B, Demers LM, Hamilton C, et al. Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: interim feasibility and biomarkers analysis from a clinical trial. *European Journal of Clinical Nutrition* 2012;**66**(8): 878–84. PUBMED: 22669332]

Schirmer 2007 {published data only}

Schirmer MA, Phinney SD. Gamma-linolenate reduces weight regain in formerly obese humans. *Journal of Nutrition* 2007;**137**(6):1430–5. PUBMED: 17513402]

SCIMO - von Schacky 1999 {published and unpublished data}

Angerer P, Kothny W, Stork S, von Schacky C. Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries. *Cardiovascular Research* 2002;54(1):183–90.

* von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebocontrolled trial. *Annals of Internal Medicine* 1999;**130**(7): 554–62.

von Schacky C, Baumann K, Angerer P. The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications. *Lipids* 2001;**36 Suppl**:S99–102.

Shinto 2014 {published data only}

NCT00090402. Fish oil and alpha lipoic acid in treating Alzheimer's Disease. clinicaltrials.gov/ct2/show/NCT00090402 (first posted 26 August 2014).

* Shinto L, Quinn J, Montine T, Dodge HH, Woodward W, Baldauf-Wagner S, et al. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. *Journal of Alzheimer's Disease* 2014;**38** (1):111–20. PUBMED: 24077434]

SHOT - Eritsland 1996 {published and unpublished data}

Eritsland J, Arnesen H, Berg K, Seljeflot I, Abdelnoor M. Serum Lp(a) lipoprotein levels in patients with coronary artery disease and the influence of long-term n-3 fatty acid supplementation. *Scandinavian Journal of Clinical and Laboratory Investigation* 1995;**55**(4):295–300.

* Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. *American Journal of Cardiology* 1996;77(1):31–6.

Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of supplementation with n-3 fatty acids on graft patency in patients undergoing coronary artery bypass operation. Results from SHOT study. *European Heart Journal* 1994;**15**:29.

Eritsland J, Arnesen H, Seljeflot I, Hostmark AT. Longterm metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. *American Journal of Clinical Nutrition* 1995;**61**(4):831–6.

Eritsland J, Arnesen H, Seljeflot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagulation & Fibrinolysis* 1995;**6**(1): 17–22.

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids. *Fibrinolysis* 1994;8(2):120–5.

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H, Torjesen PA. Long-term effects of n-3 fatty acids on serum lipids and glycaemic control. *Scandinavian Journal of Clinical and Laboratory Investigation* 1994;**54**(4):273–80.

Eritsland J, Seljeflot I, Arnesen H, Abdelnoor M. Long-term effects of fish oil supplementation in patients with coronary artery disease: influence on lipoproteins, coagulation and fibrinolysis [abstract]. *Thrombosis Research* 1992;**65**:75. Eritsland J, Seljeflot I, Arnesen H, Abdelnoor M. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids. *Thrombosis and Haemostasis* 1993;**69**: 1065.

Eritsland J, Seljeflot I, Arnesen H, Westvik AB, Kierulf P. Effect of long-term, moderate-dose supplementation with omega-3 fatty acids on monocyte procoagulant activity and release of interleukin-6 in patients with coronary artery disease. *Thrombosis Research* 1995;77(4):337–46.

Sianni 2013 {published data only}

Sianni A, Matsoukis I, Ganotopoulou A, Paraskevas P, Asimis A, Tsivilis N, et al. PP128-sun effect of omega 3 fatty acids in patients with hypertension and atrial fibrillation. *Clinical Nutrition* 2013;**32**(Suppl 1):S70–1.

SMART Tapsell 2013 {published data only}

Anil S, Charlton KE, Tapsell LC, Probst Y, Ndanuko R, Batterham MJ. Identification of dietary patterns associated with blood pressure in a sample of overweight Australians. *Journal of Human Hypertension* 2016;**30**(11):672–8. DOI: 10.1038/jhh.2016.10

Tapsell LC, Batterham MJ, Charlton KE. Effect of dietary restriction and n-3 PUFA supplementation on insulin resistance in obese adults. *FASEB Journal* 2010;**24**:733.9. * Tapsell LC, Batterham MJ, Charlton KE, Neale EP, Probst YC, O'Shea JE, et al. Foods, nutrients or whole diets: effects of targeting fish and LCn3PUFA consumption in a 12mo weight loss trial. *BMC Public Health* 2013;**13**:1231. PUBMED: 24369765]

SOFA 2006 {published and unpublished data}

Brouwer IA, Katan MB, Schouten EG, Camm AJ, Hauer RNW, Wever EFD, et al. Rationale and design of a clinical trial on n-3 fatty acids and cardiac arrhythmia (SOFA). *Annals of Nutrition & Metabolism* 2001;**45**(Suppl 1):79. Brouwer IA, Raitt MH, Dullemeijer C, Kraemer DF, Zock PL, Morris C, et al. Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. *European Heart Journal* 2009;**30**(7):820–6.

* Brouwer IA, Zock PL, Camm AJ, Böcker D, Hauer

RN, Wever EF, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA* 2006;**295**(22):2613–9.

Brouwer IA, Zock PL, Wever EFD, Hauer RNW, Camm AJ, Bocker D, et al. Rationale and design of a randomised controlled clinical trial on supplemental intake of n-3 fatty acids and incidence of cardiac arrhythmia: SOFA. *European Journal of Clinical Nutrition* 2003;57:1323–30.

Sofi 2010 {published data only}

Sofi F, Giangrandi I, Cesari F, Corsani I, Abbate R, Gensini GF, et al. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients: a preliminary study. *International Journal of food Sciences and Nutrition* 2010;**61** (8):792–802. PUBMED: 20465434]

STARS 1992 {published and unpublished data}

Blann AD, Jackson P, Bath PM, Watts GF. Von Willebrand factor, a possible indicator of endothelial cell damage, decreases during long-term compliance with a lipid-lowering diet. *Journal of Internal Medicine* 1995;237:557–61.

Watts GF. Nutritional, metabolic, and genetic determinants of the progression of coronary beart disease. STARS Group.

Watts GF. Nutritional, metabolic, and genetic determinants of the progression of coronary heart disease. STARS Group. Journal of Cardiovascular Pharmacology 1995;25 (Suppl 4): S11–9.

Watts GF, Brunt JNH, Coltart DJ, Lewis B. The St. Thomas Atherosclerosis Regression Study (STARS). *Atherosclerosis* 1992;**97**:231.

Watts GF, Jackson P, Burke V, Lewis B. Dietary fatty acids and progression of coronary artery disease in men. *American Journal of Clinical Nutrition* 1996;64:202–9.

Watts GF, Jackson P, Mandalia S, Brunt JN, Lewis ES, Coltart DJ, et al. Nutrient intake and progression of coronary artery disease. *American Journal of Cardiology* 1994;73(5):328–32.

* Watts GF, Lewis B, Brunt JN, Lewis ES, Coltart DJ, Smith LD, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). *Lancet* 1992;**339**(8793):563–9.

Watts GF, Lewis B, Brunt JNH, Swan AV. Coronary atheroma regression trials. *Lancet* 1992;**339**(i):1241–3. Watts GF, Lewis B, Jackson P, Burke V, Lewis ES, Brunt JN, et al. Relationships between nutrient intake and progression/regression of coronary atherosclerosis as assessed by serial quantitative angiography. *Canadian Journal of Cardiology* 1995;**11**(Suppl G):110G–4G.

Watts GF, Mandalia S, Brunt JN, Slavin BM, Coltart DJ, Lewis B. Independent associations between plasma lipoprotein subfraction levels and the course of coronary artery disease in the St. Thomas' Atherosclerosis Regression Study (STARS). *Metabolism: Clinical and Experimental* 1993;42:1461–7.

Watts GF, Mandalia S, Slavin BM, Brunt JN, Coltart DJ, Lewis B. Metabolic determinants of the course of coronary artery disease in men. *Clinical Chemistry* 1994;**40**(12): 2240–6

Stoll 2001 {published data only}

NCT00010868. Omega-3 fatty acids in bipolar disorder. clinicaltrials.gov/ct2/show/NCT00010868 (first posted 5 February 2001).

STRENGTH {published data only}

NCT02104817. Outcomes study to assess statin residual risk reduction with EpaNova in high CV risk patients with hypertriglyceridemia (STRENGTH). clinicaltrials.gov/ct2/show/NCT02104817 2014.

SU.FOL.OM3 Galan 2010 {published and unpublished data}

Ahluwalia N, Blacher J, Szabo De Edelenyi F, Faure P, Julia C, Hercberg S, et al. Prognostic value of multiple emerging biomarkers in cardiovascular risk prediction in patients with stable cardiovascular disease. *Atherosclerosis* 2013;**228**(2): 478–84.

Andreeva VA, Galan P, Torres M, Julia C, Hercberg S, Kesse-Guyot E. Supplementation with B vitamins or n-3 fatty acids and depressive symptoms in cardiovascular disease survivors: ancillary findings from the SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids (SU.FOL.OM3) randomized trial. *American Journal of Clinical Nutrition* 2012;**96**(1):208–14.

Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. *American Journal of Clinical Nutrition* 2011;**94**(1):278–86.

Andreeva VA, Latarche C, Hercberg S, Briancon S, Galan P, Kesse-Guyot E. B vitamin and/or n-3 fatty acid supplementation and health-related quality of life: ancillary findings from the SU.FOL.OM3 randomized trial. *PLoS One* 2014;**9**(1):e84844.

Andreeva VA, Touvier M, Kesse-Guyot E, Julia C, Galan P, Hercberg S. B vitamin and/or omega-3 fatty acid supplementation and cancer: ancillary findings from the supplementation with folate, vitamins B6 and B12, and/or omega-3 fatty acids (SU.FOL.OM3) randomized trial. *Archives of Internal Medicine* 2012;**172**(7):540–7.

Arnaud J, Bost M, Vitoux D, Labarere J, Galan P, Faure H, et al. Effect of low dose antioxidant vitamin and trace element supplementation on the urinary concentrations of thromboxane and prostacyclin metabolites. *Journal of the American College of Nutrition* 2007;**26**(5):405–11.

Astorg P, Bertrais S, Alessandri JM, Guesnet P, Kesse-Guyot E, Linard A, et al. Long-chain n-3 fatty acid levels in baseline serum phospholipids do not predict later occurrence of depressive episodes: a nested case-control study within a cohort of middle-aged French men and women. *Prostaglandins Leukotrienes & Essential Fatty Acids* 2009;81(4):265–71.

Astorg P, Couthouis A, Bertrais S, Arnault N, Meneton P, Guesnet P, et al. Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women.

Prostaglandins Leukotrienes & Essential Fatty Acids 2008;78 (3):171–82.

Blacher J, Czernichow S, Paillard F, Ducimetiere P, Hercberg S, Galan P, et al. Cardiovascular effects of B-vitamins and/ or N-3 fatty acids: the SU.FOL.OM3 trial. *International Journal of Cardiology* 2013;**167**(2):508–13.

Blacher J, Safar ME, Ly C, Szabo De Edelenyi F, Hercberg S, Galan P. Blood pressure variability: cardiovascular risk integrator or independent risk factor. *Journal of Human Hypertension* 2015;**29**(2):122–6.

Czernichow S, Bruckert E, Oppert JM, Bertrais S, Paillard F, Astorg P, et al. Intake of added oils and fats among middle-aged French adults: relationships with educational level and region of residence. *Journal of the American Dietetic Association* 2005;**105**(12):1889–94.

Fezeu LK, Laporte F, Kesse-Guyot E, Andreeva VA, Blacher J, Hercberg S, et al. Baseline plasma fatty acids profile and incident cardiovascular events in the SU.FOL.OM3 trial: the evidence revisited. *PLoS One* 2014;**9**(4):e92548. Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The SU.FOL.OM3 study: a secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or Omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics. *Trials* 2008;**9**:35.

Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The SU.FOL.OM3 study: a secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics. *Trials* 2008;9:35. DOI: 10.1186/1745-6215-9-35

Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The scientific basis of the SU.FOL.OM3 study: a secondary intervention trial of folate, B6 and B12 vitamins and/or omega3 fatty acid supplements in the prevention of recurrent ischemic events. *Sang Thrombose Vaisseaux* 2009; **21**(4):207–13.

Galan P, Briançon S, Blacher J, Czernichow S, Hercberg S. The scientific basis of the SU.FOL.OM3 study: a secondary intervention trial of folate, B6 and B12 vitamins and/or omega3 fatty acid supplements in the prevention of recurrent ischemic events [Bases scientifiques de l'étude SUFOLOM3: essai de prévention secondaire visant à tester l'impact d'une supplémentation en folates, vitamines B6 et B12 et/ ou acides gras oméga–3 dans la prévention de la récidive de pathologies ischémiques]. Sang Thrombose Vaisseaux 2009;21(4):207–13.

* Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S, SU.FOL.OM3 Collaborative Group. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *BMJ* 2010;**341**:c6273. DOI: 10.1136/bmj.c6273 Galan P, de Bree A, Mennen L, Potier de Courcy G, Preziozi P, Bertrais S, et al. Background and rationale of the SU.FOL.OM3 study: double-blind randomized placebo-controlled secondary prevention trial to test the impact of

supplementation with folate, vitamin B6 and B12 and/or omega-3 fatty acids on the prevention of recurrent ischemic events in subjects with atherosclerosis in the coronary or cerebral arteries. *Journal of Nutrition, Health & Aging* 2003; 7(6):428–35.

Julia C, Meunier N, Touvier M, Ahluwalia N, Sapin V, Papet I, et al. Dietary patterns and risk of elevated C-reactive protein concentrations 12 years later. *British Journal of Nutrition* 2013;**110**(4):747–54.

Julia C, Touvier M, Meunier N, Papet I, Galan P, Hercberg S, et al. Intakes of PUFAs were inversely associated with plasma C-reactive protein 12 years later in a middle-aged population with vitamin E intake as an effect modifier. *Journal of Nutrition* 2013;**143**(11):1760–6.

Kesse-Guyot E, Peneau S, Hercberg S, Galan P, Vogt L, Escande M, et al. Thirteen-year prospective study between fish consumption, long-chain n-3 fatty acids intakes and cognitive function. *Journal of Nutrition, Health and Aging* 2011;**15**(2):115–20.

Latreille J, Kesse-Guyot E, Malvy D, Andreeva V, Galan P, Tschachler E, et al. Association between dietary intake of n-3 polyunsaturated fatty acids and severity of skin photoaging in a middle-aged Caucasian population. *Journal of Dermatological Science* 2013;72(3):233–9.

Latreille J, Kesse-Guyot E, Malvy D, Andreeva V, Galan P, Tschachler E, et al. Dietary monounsaturated fatty acids intake and risk of skin photoaging. *PLoS One* 2012;7(9): e44490.

Pouchieu C, Chajes V, Laporte F, Kesse-Guyot E, Galan P, Hercberg S, et al. Prospective associations between plasma saturated, monounsaturated and polyunsaturated fatty acids and overall and breast cancer risk - modulation by antioxidants: a nested case-control study. *PLoS One* 2014;**9** (2):e90442.

Szabo De Edelenyi F, Vergnaud AC, Ahluwalia N, Julia C, Hercberg S, Blacher J, et al. Effect of B-vitamins and n-3 PUFA supplementation for 5 years on blood pressure in patients with CVD. *British Journal of Nutrition* 2012;**107** (6):921–7.

Touvier M, Kesse-Guyot E, Andreeva VA, Fezeu L, Charnaux N, Sutton A, et al. Modulation of the association between plasma intercellular adhesion molecule-1 and cancer risk by n-3 PUFA intake: a nested case-control study. *American Journal of Clinical Nutrition* 2012;**95**(4):944–50. Vesin C, Galan P, Gautier B, Czernichow S, Hercberg S, Blacher J. Control of baseline cardiovascular risk factors in the SU-FOL-OM3 study cohort: does the localization of the arterial event matter?. *European Journal of Cardiovascular Prevention & Rehabilitation* 2010;**17**(5):541–8. de Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. *European Journal of*

Søndergaard 2003 {published and unpublished data}

Clinical Nutrition 2004;58(5):732-44.

Sondergaard E, Moller JE, Egstrup K. Effect of dietary intervention and lipid-lowering treatment on brachial vasoreactivity in patients with ischemic heart disease and

hypercholesterolemia. American Heart Journal 2003;145 (5):F19

Tande 2016 {published data only}

Tande KS, Vo TD, Lynch BS. Clinical safety evaluation of marine oil derived from Calanus finmarchicus. *Regulatory Toxicology and Pharmacology:* RTP 2016;**80**:25–31. PUBMED: 27233921]

Tay 2015 {published data only}

* Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. *American Journal of Clinical Nutrition* 2015;**102**(4):780–90.

Tay J, Thompson CH, Luscombe-Marsh ND, Noakes M, Buckley JD, Wittert GA, et al. Long-term effects of a very low carbohydrate compared with a high carbohydrate diet on renal function in individuals with type 2 diabetes: a randomized trial. *Medicine* 2015;**94**(47):e2181. DOI: 10.1097/MD.0000000000002181

THIS DIET - Tuttle 2008 {published and unpublished data}

Tuttle KR, Shuler LA, Packard DP, Milton JE, Daratha KB, Bibus DM, et al. Comparison of low-fat versus Mediterranean-style dietary intervention after first myocardial infarction (from The Heart Institute of Spokane Diet Intervention and Evaluation Trial). *American Journal of Cardiology* 2008;**101**(11):1523–30. PUBMED: 18489927]

VITAL {published data only}

Bassuk SS, Manson JE, Lee IM, Cook NR, Christen WG, Bubes VY, et al. Baseline characteristics of participants in the VITamin D and OmegA-3 TriaL (VITAL). *Contemporary Clinical Trials* 2016;47:235–43.

Gold DR, Litonjua AA, Carey VJ, Manson JE, Buring JE, Lee IM, et al. Lung VITAL: rationale, design, and baseline characteristics of an ancillary study evaluating the effects of vitamin D and/or marine omega-3 fatty acid supplements on acute exacerbations of chronic respiratory disease, asthma control, pneumonia and lung function in adults. *Contemporary Clinical Trials* 2016;47:185–95. Gold DR, Luttmann-Gibson H, Litonjua AA, Friedenberg G, Gordon D, Lee IM, et al. Baseline chronic obstructive pulmonary disease in the lung vitamin D and omega-3 trial. *American Journal of Respiratory and Critical Care Medicine* 2014;189:D44 COPD.

Kang JH, Grodstein F, Manson JAE. Cognitive substudy of the vitamin d and omega-3 trial (VITAL-Cog): design of a large randomized trial of omega-3 and vitamin d supplements in relation to cognitive change. *Alzheimer's & Dementia* 2015;1:608.

LeBoff MS, Yue AY, Copeland T, Cook NR, Buring JE, Manson JE. VITAL-bone health: rationale and design of two ancillary studies evaluating the effects of vitamin D and/or omega-3 fatty acid supplements on incident fractures and bone health outcomes in the VITamin D and OmegA-3 TriaL (VITAL). *Contemporary Clinical Trials* 2015;41:

Manson JAE. Vitamin D and cancer and cardiovascular disease: ready for prime time?. *Menopause* 2010;17(6):

1215

Manson JE. Vitamin D and the heart: why we need largescale clinical trials. *Cleveland Clinic Journal of Medicine* 2010;77(12):903–10.

* Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, et al. The VITamin D and omegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemporary Clinical Trials* 2012; 33(1):159–71.

Pradhan AD, Manson JE. Update on the Vitamin D and OmegA-3 trial (VITAL). *Journal of Steroid Biochemistry & Molecular Biology* 2016;**155**(Pt B):252–6.

Weinstock-Guttman 2005 {published data only}

Weinstock-Guttman B, Baier M, Park Y, Feichter J, Lee-Kwen P, Gallagher E, et al. Low fat dietary intervention with n-3 fatty acid supplementation in multiple sclerosis patients. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2005; 73:397–404. DOI: 10.1016/j.plefa.2005.05.024

WHI 2006 {published data only}

Anderson G, Cummings S, Freedman LS, Furberg C, Henderson M, Johnson SR, et al. Design of the Women's Health Initiative clinical trial and observational study. Controlled Clinical Trials 1998;19(1):61–109.

Anderson GL, Manson J, Wallace R, Lund B, Hall D, Davis S, et al. Implementation of the Women's Health Initiative study design. *Annals of Epidemiology* 2003;**13**(9 Suppl): S5–17.

Beresford SA, Johnson KC, Ritenbaugh C, Lasser NL, Snetselaar LG, Black HR, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;**295**(6):643–54.

Bowen D, Ehret C, Pedersen M, Snetselaar L, Johnson M, Tinker L, et al. Results of an adjunct dietary intervention program in the Women's Health Initiative. Journal of the American Dietetic Association 2002;102(11):1631-7. Carty CL, Kooperberg C, Neuhouser ML, Tinker L, Howard B, Wactawski-Wende J, et al. Low-fat dietary pattern and change in body-composition traits in the Women's Health Initiative Dietary Modification Trial. American Journal of Clinical Nutrition 2011;93:516-24. Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Annals of Epidemiology 2003;13(9 Suppl):S122-8. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, et al. The Women's Health Initiative recruitment methods and results. Annals of Epidemiology 2003;13(9 Suppl):S18-77.

Hebert JR, Patterson RE, Gorfine M, Ebbeling CB, St Jeor ST, Chlebowski RT, et al. Differences between estimated caloric requirements and self-reported caloric intake in the Women's Health Initiative. *Annals of Epidemiology* 2003;**13** (9):629–37.

Howard BV. Dietary fat and cardiovascular disease: putting

the Women's Health Initiative in perspective. *Nutrition Metabolism & Cardiovascular Diseases* 2007;**17**(3):171–4. Howard BV, Manson JE, Stefanick ML, Beresford SA, Frank G, Jones B, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. *JAMA* 2006;**295**(1):39–49.

* Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;**295**(6):655–66.

Neuhouser ML, Tinker L, Shaw PA, Schoeller D, Bingham SA, Horn LV, et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. *American Journal of Epidemiology* 2008;**167**(10): 1247–59.

Patterson RE, Kristal A, Rodabough R, Caan B, Lillington L, Mossavar-Rahmani Y, et al. Changes in food sources of dietary fat in response to an intensive low-fat dietary intervention: early results from the Women's Health Initiative. *Journal of the American Dietetic Association* 2003; **103**(4):454–60.

Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, gurs-Collins T, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Annals of Epidemiology 1999;9(3):178–87.

Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;**295**(6):629–42.

Prentice RL, Thomson CA, Caan B, Hubbell FA, Anderson GL, Beresford SA, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. *Journal of the National Cancer Institute* 2007;**99**(20):1534–43.

Ritenbaugh C, Patterson RE, Chlebowski RT, Caan B, Fels-Tinker L, Howard B, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Annals of Epidemiology* 2003; **13**(9 Suppl):S87–97.

Robinson JG, Wallace R, Safford MM, Pettinger M, Cochrane B, Ko MG, et al. Another treatment gap: restarting secondary prevention medications: the Women's Health Initiative. *Journal of Clinical Lipidology* 2010;4: 36–45.

Rossouw JE, Finnegan LP, Harlan WR, Pinn VW, Clifford C, McGowan JA. The evolution of the Women's Health Initiative: perspectives from the NIH. *Journal of the American Medical Women's Association* 1995;**50**(2):50–5. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Controlled Clinical Trials* 1998;**19**(1):61–109. Tinker LF, Bonds DE, Margolis KL, Manson JE, Howard BV, Larson J, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary

modification trial. Archives of Internal Medicine 2008;168 (14):1500-11

Tinker LF, Perri MG, Patterson RE, Bowen DJ, McIntosh M, Parker LM, et al. The effects of physical and emotional status on adherence to a low-fat dietary pattern in the Women's Health Initiative. *Journal of the American Dietetic Association* 2002;**102**(6):789–800.

Tinker LF, Rosal MC, Young AF, Perri MG, Patterson RE, Van Horn L, et al. Predictors of dietary change and maintenance in the Women's Health Initiative Dietary Modification Trial. *Journal of the American Dietetic Association* 2007;**107**(7):1155–66.

Women's Health Initiative Study Group. Dietary adherence in the Women's Health Initiative Dietary Modification
Trial. *Journal of the American Dietetic Association* 2004;**104**(4):654–8

Zhang 2016 {published data only}

Zhang YP, Miao R, Li Q, Wu T, Ma F. Effects of DHA supplementation on hippocampal volume and cognitive function in older adults with mild cognitive impairment: A 12-month randomized, double-blind, placebo-controlled trial. *Journal of Alzheimer's Disease* 2016;**55**(2):497–507.

References to ongoing studies

AC Omega3 {published data only}

ACTRN12614000732684. The Aboriginal cardiovascular omega-3 randomised controlled trial [The effect of omega-3 supplementation on adverse cardiovascular (CV) events among Indigenous Australians with stable coronary artery disease: a randomized controlled trial]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366337 (date registered 10 July 2014).

ACTRN12610000594022 {published data only}

ACTRN12610000594022. Fish oil as adjunct therapy for periodontitis [Clinical efficacy of fish oil as adjunct therapy for patients with chronic periodontitis]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=335470 (date registered 23 July 2010).

ACTRN12613000034730 {published data only}

ACTRN12613000034730. Intervention of testosterone & fish oil as a possible strategy for the prevention of Alzheimer's Disease [A 56 week, double-blind, randomised, placebo-controlled trial to determine the efficacy of testosterone, with and without DHA supplementation in PiB positive men with subjective memory complaints as a strategy to prevent the development of Alzheimer's disease]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id= 363372 (date registered 14 January 2013).

AFORRD {published and unpublished data}

Holman RR, Paul S, Farmer A, Tucker L, Stratton IM, Neil HA, et al. Atorvastatin in factorial with omega-3 EE90 risk reduction in diabetes (AFORRD): a randomised controlled trial. *Diabetologia* 2009;**52**(1):50–9.

Neil HA, Ceglarek U, Thiery J, Paul S, Farmer A, Holman RR. Impact of atorvastatin and omega-3 ethyl esters 90 on plasma plant sterol concentrations and cholesterol synthesis

in type 2 diabetes: a randomised placebo controlled factorial trial. *Atherosclerosis* 2010;**213**(2):512–7.

Beyond Aging Project {published data only}

Cockayne NL, Duffy SL, Bonomally R, English A, Amminger PG, Mackinnon A, et al. The Beyond Ageing Project Phase 2--a double-blind, selective prevention, randomised, placebo-controlled trial of omega-3 fatty acids and sertraline in an older age cohort at risk for depression: study protocol for a randomized controlled trial. *Trials* 2015;16:247.

Chandrakala 2010 {published data only (unpublished sought but not used)}

Chandrakala G, Arpana G, Rao PV. Long-term effects of a reduced fat diet intervention in pre-diabetes. professional.diabetes.org/meeting/scientific-sessions/70th-scientific-sessions-2010 (accessed before 11 April 2018). Chandrakala G, Arpana G, Sreenivas T, Rao PV. Low-fat (<20%) diets prevent type 2 diabetes mellitus. *Diabetes* 2012;**61**:A190.

n-3 for Vascular Cognitive Aging {published data only}

Shinto L, Silbert LC, Dodge HH, Quinn JF, Howieson D, Kaye J, et al. Omega 3 fatty acids for the prevention of vascular cognitive aging: methods and rationale for a phase II trial. Alzheimer's & Dementia 2015:P2–305.

n-3 on plasma lipid {published data only}

ChiCTR-TRC-12002014. Influence of different source of n-3 fatty acid on plasma lipid in moderately hypercholesterolemia subject and the valid dosage. www.chictr.org.cn/hvshowproject.aspx?id=2374 (date last refreshed on 3 May 2015).

NCT00309439 {published data only}

NCT00309439. ALA and prostate cancer. clinicaltrials.gov/ct2/show/NCT00309439 (first posted 31 March 2006).

NCT00410020 {published data only}

NCT00410020. Arrhythmia prevention with an alphalinolenic enriched diet. clinicaltrials.gov/ct2/show/ NCT00410020 (first posted 12 December 2006).

NCT01047449 {published data only}

NCT01047449. Improving the results of heart bypass surgery using new approaches to surgery and medication (SUPERIORSVG). clinicaltrials.gov/ct2/show/NCT01047449 (first posted 13 January 2010).

NCT01513252 {published data only}

NCT01513252. Long-term effects of interventional strategies to prevent cognitive decline in elderly (MAPT-PLUS). clinicaltrials.gov/ct2/show/NCT01513252 (first posted 20 January 2012).

NCT01784042 {published data only}

NCT01784042. Dietary energy restriction and omega-3 fatty acids on mammary tissue. clinicaltrials.gov/ct2/show/NCT01784042 (first posted 5 February 2013).

NCT02128763 {published data only}

NCT02128763. Dry eye assessment and management study (DREAM). clinicaltrials.gov/ct2/show/NCT02128763 (first posted 1 May 2014).

NCT02211560 {published data only}

NCT02211560. Investigating a phosphatidylserine based dietary approach for the management of mild cognitive impairment. clinicaltrials.gov/ct2/show/NCT02211560 (first posted 7 August 2014).

NCT02295059 {published data only}

NCT02295059. Omega 3 fatty acids and ERPR(-)HER2 (+/-) breast cancer prevention. clinicaltrials.gov/ct2/show/NCT02295059 (first posted 20 November 2014).

NCT02676466 {published data only}

NCT02676466. The ENRGISE pilot study (ENRGISE). clinicaltrials.gov/ct2/show/NCT02676466 (first posted 8 February 2016).

NCT02719327 {published data only}

NCT02719327. Brain amyloid and vascular effects of eicosapentaenoic acid (BRAVE-EPA). clinicaltrials.gov/ct2/show/NCT02719327 (first posted 25 March 2016).

OMEMI {published data only}

Laake K, Myhre P, Nordby LM, Seljeflot I, Abdelnoor M, Smith P, et al. Effects of omega 3 supplementation in elderly patients with acute myocardial infarction: design of a prospective randomized placebo controlled study. *BMC Geriatrics* 2014;**14**:74. http://www.biomedcentral.com/1471–2318/14/74]

* Laake K, Seljeflot I, Schmidt EB, Myhre P, Tveit A, Arnesen H, et al. Serum fatty acids, traditional risk factors, and comorbidity as related to myocardial injury in an elderly population with acute myocardial infarction. *Journal of Lipids* 2016;**2016**:4945720. http://dx.doi.org/10.1155/2016/4945720]

REDUCE-IT {published data only}

Bhatt DL, Steg G, Brinton EA, Jacobson TA, Miller M, Tardif J-C, et al. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial. *Clinical Cardiology* 2017;**40**:138–48. DOI: 10.1002/clc.22692

seAFOOD {published data only}

* Hull MA, Sandell AC, Montgomery AA, Logan RF, Clifford GM, Rees CJ, et al. A randomized controlled trial of eicosapentaenoic acid and/or aspirin for colorectal adenoma prevention during colonoscopic surveillance in the NHS Bowel Cancer Screening Programme (The seAFOod Polyp Prevention Trial): study protocol for a randomized controlled trial. *Trials* 2013;14:237.

ISRCTN05926847. The seAFOod (Systematic Evaluation of Aspirin and Fish Oil) polyp prevention trial. www.isrctn.com/ISRCTN05926847 (data assigned 6 May 2011).

UMIN000012825 {published data only}

UMIN000012825. Effect of polysaturated fatty acids on vascular healing process in hyper-cholesterolemic patients with acute coronary syndrome. upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000014981 (first posted 1 February 2014).

Additional references

4S Trial 1994

4S trial authors. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**(8934): 1383–9.

Abdelhamid 2017

Abdelhamid A, Hooper L, Welch A. Polyunsaturated fatty acids for musculoskeletal health and functional status in older adults. PROSPERO 2017; Vol. www.crd.york.ac.uk/prospero/display`record.php?RecordID=79211: CRD42017079211.

Abdelhamid 2018

Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2018, Issue 6. DOI: 10.1002/14651858.CD003177.pub3

Berkley 1995

Berkley CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Statistics in Medicine* 1995;**14**(4):395–411.

Bhatnagar 2016

Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. *Heart* 2016;**102**:1945–1952. DOI: http://dx.doi.org/10.1136/heartjnl-2016-309573

Brown 2017

Brown T, Song F, Wang X, Brainard J, Hooper L. Dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus. PROSPERO 2017:CRD42017064110.

Burr 1989

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;**2**(8666):757–61.

Calder 2012

Calder PC. Mechanisms of action of (n-3) fatty acids. Journal of Nutrition 2012;**142**(3):592S–9S. DOI: 10.3945/ %E2%80%8Bjn.111.155259

Carandang 2006

Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, Wolf PA. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA* 2006;**296**(24):2939–46. DOI: 10.1001/jama.296.24.2939

Carlisle 2017

Carlisle JB. Data fabrication and other reasons for non-random sampling in5087 randomised, controlled trials in anaesthetic and general medical journals. *Anaesthesia* 2017; **72**:944–952. DOI: 10.1111/anae.13938

de Souza 2015

de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-

analysis of observational studies. *BMJ* 2015;**351**:h3978. DOI: https://doi.org/10.1136/bmj.h3978

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Feigin 2014

Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; **383**:245–55. DOI: http://dx.doi.org/10.1016/S0140-6736 (13)61953-4

Friedewald 1972

Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;**18**(6):499–502.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 26 August 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Hanson 2017a

Hanson S, Biswas P, Jimoh OF, O'Brien A, Hooper L, Abdelhamid A, et al. Dietary polyunsaturated fat for prevention and treatment of depression and anxiety. PROSPERO 2017:CRD42017056092.

Hanson 2017b

Hanson S, Thorpe G, Winstanley L, Abdelhamid A, Hooper L. Effects of supplementary dietary polyunsaturated fat on cancer incidence. PROSPERO 2017:CRD42017056109.

Hegsted 1965

Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. *American Journal of Clinical Nutrition* 1965;17(5): 281–95

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews

of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hooper 2006

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ* 2006;**322**:752. DOI: https://doi.org/10.1136/bmj.38755.366331.2F

Hooper 2015a

Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database of Systematic Reviews* 2015, Issue 6. DOI: 10.1002/14651858.CD011737

Hooper 2015b

Hooper L, Abdelhamid A, Bunn D, Brown T, Summerbell CD, Skeaff DM. Effects of total fat intake on body weight. *Cochrane Database of Systematic Reviews* 2015, Issue 8. DOI: 10.1002/14651858.CD011834

Hooper 2018

Hooper L, Al-Khudairy L, Abdelhamid AS, Rees K, Brainard JS, Brown TJ, et al. Omega-6 fats for the prevention and treatment of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2018, Issue 6. DOI: 10.1002/14651858.CD011094.pub3

Jimoh 2017

Jimoh OF, Brainard J, Deane KA, Biswas P, Donaldson D, Hooper L. Dietary polyunsaturated fat for prevention and treatment of neurocognitive disorders. PROSPERO 2017: CRD42017019049.

Keys 1950

Keys A, Mickelsen O, Miller EVO, Carleton B. The relation in man between cholesterol levels in the diet and in the blood. *Science* 1950;**112**:79–81.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lozano 2012

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2095–128. DOI: 10.1016/S0140-6736(12)61728-0.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS* 2009;6(7):e1000097. DOI: 10.1371/journal.pmed1000097

Mozaffarian 2010

Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Medicine* 2010;7(3): e1000252. DOI: 10.1371/journal.pmed.1000252.

Ohwada 2016

Ohwada T, Yokokawa T, Kanno Y, Hotsuki Y, Sakamoto T, Watanabe K, et al. Vascular composition data supporting the role of N-3 polyunsaturated fatty acids in the prevention of cardiovascular disease events. *Data Brief* 2016;7:1237–47. DOI: http://dx.doi.org/10.1016/j.dib.2016.03.101

Oliver 1953

Oliver MF, Boyd GS. The plasma lipids in coronary artery disease. *British Heart Journal* 1953;**15**:387–90.

ORISK 2-2017

ClinRisk Ltd. QRISK[®]2-2017 risk calculator. qrisk.org/2017/index.php (accessed before 11 April 2018).

Ramsden 2010

Ramsden CE, Hibbeln JR, Majchrzak SF, Davis JM. N-6 fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHD risk: a meta-analysis of randomised controlled trials. *British Journal of Nutrition* 2010;**104**(11):1586–600. DOI: 10.1017/S0007114510004010

RevMan 2014 [Computer program]

The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2014.

Ricci 2018

Ricci C, Baumgartner J, Zec M, Kruger HS, Smuts CM. Type of dietary fat intakes in relation to all-cause and cause-specific mortality in US adults: an iso-energetic substitution analysis from the American National Health and Nutrition Examination Survey linked to the US mortality registry. *British Journal of Nutrition* 2018;**119**(4):456–63. DOI: 10.1017/S0007114517003889

Roberts 2015

Roberts I, Ker K, Edwards P, Beecher D, Manno D, Sydenham E. The knowledge system underpinning healthcare is not fit for purpose and must change. *BMJ* 2015;**350**:h2463. DOI: http://dx.doi.org/10.1136/bmj.h2463

Russo 2009

Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical implications in cardiovascular prevention. *Biochemical Pharmacology* 2009;77(6):937–46.

Savovic 2012

Savovic J, Jones H, Altman D, Harris R, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. Health Technology Assessment 2012;16:1–82.

Schultz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Sharp 1998

Sharp S. Meta-analysis regression. *Stata Technical Bulletin* 1998;**42**:16–22.

Simopoulos 2016

Simopoulos AP. An increase in the omega-6/omega-3 fatty acid ratio increases the risk for obesity. *Nutrients* 2016;**8**(3): 128. DOI: 10.3390/nu8030128

Sterne 2011

Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Thorpe 2017

Thorpe G, Ajabnoor S, Ahmed Z, Abdelhamid A, Hooper L. Dietary polyunsaturated fat for prevention and treatment of inflammatory bowel disease. PROSPERO 2017: CRD42017068704.

WHO 2004

World Health Organization. World Health Statistics. www3.who.int/whosis 2004.

WHO 2016

World Health Organization. Cardiovascular diseases (CVDs). Fact sheet number 317. www.who.int/mediacentre/factsheets/fs317/en/reviewed June 2016: (accessed 26 July 2016).

WHO/FAO 2008

Joint FAO/WHO Expert Consultation on Fats, Fatty Acids in Human Nutrition. Interim summary of conclusions and dietary recommendations on total fat & fatty acids. www.who.int/nutrition/topics/ FFA_interim_recommendations/en/ 10 – 14 November 2008; Vol. WHO, Geneva.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz K, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008; **336**:601–5.

References to other published versions of this review

Abdelhamid 2016

Abdelhamid A, Martin N, Bridges C, Song F, Deane KHO, Hooper L. Polyunsaturated fat intake for prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2016, Issue 9. DOI: 10.1002/14651858.CD012345

^{*} Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ahn 2016

Methods	RCT, parallel, (n3 EPA + DHA versus nil, both with statins), 12 months Summary risk of bias: moderate or high
Participants	Statin-treated CAD patients undergoing PCI N: 38 intervention, 36 control Level of risk for CVD: high Male: 63.2% intervention, 72.2% control Mean age (SD): 59.6 (9.1) intervention, 60.7 (0.8) [sic] control Age range: unclear Smokers: 36.8% intervention, 58.3% control Hypertension: 50% in both groups Medications taken by ≥ 50% of those in the control group: aspirin, clopidogrel, ACEi/ARB, beta blockers, atorvastatin Medications taken by 20%-49% of those in the control group: cilostazol Medications taken by some, but < 20% of the control group: rosuvastatin, nitrates, calcium antagonists Location: South Korea
	Ethinicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs unclear (nil) Intervention: 3 g of ω-3 PUFA containing 1395 mg of EPA and 1125 mg of DHA/d. No further details Control: unclear whether control group were given placebo or only statins Dose aim: increase 2.5 g/d EPA + DHA, 1% E n-3 Baseline PUFA unclear
	Compliance by biomarkers: no tissue fatty acids reported, but TC was reduced by 31.
	5% in intervention and by 20.9% in the control group, supporting greater PUFA intake in the intervention arm Compliance by dietary intake: not reported • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported Compliance, other methods: unclear how it was measured but reported good compliance with no numbers

Ahn 2016 (Continued)

	Inclusion basis: planned dose suggested total PUFA intake 2.5 g/d higher in intervention, or 1.13% E PUFA dose. There were no biomarker or dietary intake data to confirm this, but greater reductions in TC in the intervention arm supports. > 10% increase from assumed baseline of 6% E PUFA PUFA dose: 1.13% E Length of intervention: 12 months
Outcomes	Main trial outcome: change in atherosclerotic burden Dropouts: none Available outcomes: lipids (TG reported as median, IQR so not used), atheroma volume, neointimal volume index Response to contact: contact attempted but no response to date
Notes	Trial funding: the trial was supported by clinical research grant from Pusan National University Hospital

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation was carried out using random number tables to assign each participant to the intervention or control group
Allocation concealment (selection bias)	Low risk	Participants were assigned randomisation numbers sequentially on recruitment to the trial, and the randomisation codes were re- tained by the clinical research co-ordinator
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The personnel responsible for randomisation as well as those performing laboratory measurements were blinded to the randomisation assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention bias	Unclear risk	No details
Compliance	Low risk	No fatty acid levels reported, but TC lower in higher PUFA arm

Ahn 2016 (Continued)

Other bias	High risk	It's unclear whether the trial was placebo controlled or the control group had no in- tervention. Also, some of the SDs appear
		to be incorrectly reported

Methods	RCT, 2 x 2 (n3 ALA vs MUFA), 40 months Summary risk of bias: low
Participants	60-80 year olds with previous MI N: intervention 2409 (1197 ALA, 1212 ALA + EPA + DHA), control 2428 (1236 MUFA, 1192 EPA + DHA). All analysed in ITT analysis Level of risk for CVD: high Male: 77.9% intervention, 78.7% control Mean age (SD): 69.0 (5.6) intervention, 68.9 (5.6) control Age range: 60-80 years Smokers: 17.4% intervention, 18% control Hypertension: unclear Medications taken by ≥ 50% of those in the control group: lipid-lowering medication, antihypertensives, antithrombotics Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: antiarrythmic drugs, antidiabetic drugs Location: Netherlands Ethinicty: not reported
Interventions	Type: supplementary margarine Comparsion: ALA vs MUFA Intervention: 20 g/d of enriched margarine incorporating: 2 g ALA. 8 x 250 g margarine tubs delivered every 12 weeks Control: 20 g/d of margarine. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo Dose aim: increase 2 g/d, 1% E n-3 Baseline PUFA unclear Compliance by biomarkers: plasma cholesteryl esters had clearly higher ALA in the two ALA arms, no data for total PUFA, no serum TC reported post-baseline Compliance by dietary intake: margarine composition data - summing LA, ALA, EPA, DPA and DHA total PUFA dose in ALA margarine (compared to placebo) was +14.4% E. As planned intake was 20 g/d, intake was 2.88 g/d total PUFA, or 1.3% E from total PUFA. Total PUFA in ALA + EPA + DHA (compared to EPA + DHA margarine) was 11.3% E, or 2.26 g/d total PUFA, 1.02% E total PUFA • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • SFA intake: not reported • PUFA intake: not reported

AlphaOmega - ALA (Continued)

Apria o mega - ALM (Commuca)			
	 PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake: not reported CHO intake: not reported Sugars intake: not reported Protein intake: not reported Alcohol intake: not reported Alcohol intake: not reported Compliance, other methods: unused margarine tubs were returned- daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of participants adhered to the protocol and consumed 20.6 (2.8) g/d of margarine Inclusion basis: planned total PUFA intake 1.02 and 1.30% E higher in control than intervention, > 10% higher than assumed 6% E from total PUFA at baseline PUFA dose: 1.02% E in ALA + EPA + DHA vs EPA + DHA, 1.3% E in ALA margarine vs placebo margarine Duration of intervention: 40 months 		
Outcomes	Main trial outcome: CVD events Dropouts: 91 died, 98 discontinued intervention, 93 died, 93 discontinued control Available outcomes: deaths, MI, CVD events, VF/VT, incident CVD Response to contact: yes (data provided)		
Notes	This is a 2 x 2 trial, using ALA margarine vs MUFA margarine (this part) and EPA/DHA margarine vs MUFA margarine (the next trial). The 4 arms were ALA margarine, EPA/DHA margarine, mixture of the 2 interventions and MUFA margarine. This table represents the AL- only intervention. Where possible data represent the full trial population for each comparison (ALA margarine plus combined intervention vs MUFA margarine plus EPA/DHA margarine). As this review assesses effects of total PUFA, and doses of total PUFA were higher in the ALA arms we have omitted the EPA/DHA data when pooling would otherwise have meant that each participant was represented twice in meta-analysis Trial funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	On the computer by a random-number generator before the start of the trial	
Allocation concealment (selection bias)	Low risk	Trial author confirmed allocation was concealed from clinicians/ researchers	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The 4 types of margarine were "similar in taste, texture and colour". A trained test panel did not perceive a fishy taste or odour. Randomisation tables were stored safely	

AlphaOmega - ALA (Continued)

		under supervision
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation tables were stored safely under supervision. There was an independent statistician for data analysis Quote: "Events were coded by three members of the end-point adjudication committee who were unaware of the identity of the patient, the identity of the treating physician and the patients assigned study group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up for events. Computerised linkage with municipal registries. 2531 participants were only followed up for baseline anthropometric and medical measurements
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered in August 2005, recruitment was from 2002-2006. Outcomes papers published in 2010
Attention bias	Low risk	All participants appear to have had similar frequency and quantity of attention and follow-up
Compliance	Unclear risk	Only plasma cholesteryl esters of ALA were reported and were higher in intervention arms (unclear regarding total PUFA), no TC reported
Other bias	Low risk	None noted

Bassey 2000-Post

•	
Methods	RCT, (high PUFA GLA+DHA+EPA vs low PUFA, both with Ca), 12 months Summary risk of bias: moderate or high
Participants	Healthy postmenopausal women
	N: 21 intervention, 24 control (total randomised 57)
	Level of risk for CVD: low
	Male: 0% intervention, 0% control
	Mean age (SD): 58 (4.6) intervention, 55 (4.6) control
	Age range: 50-65 years (inclusion)
	Smokers: 20.8% intervention, 19% control
	Hypertension: not reported
	Medications taken by \geq 50% of those in the control group: not reported
	Medications taken by 20%-49% of those in the control group: not reported

Bassey 2000-Post (Continued)

	Medications taken by some, but < 20% of the control group: not reported (Women on confounding drug therapy were excluded.) Location: UK Ethinicty: not reported	
Interventions	Type: capsules Comparsion: evening primrose oil + fish oil vs nil Intervention 10 large capsules/d of efacal (Ca 1.0 g, evening primrose oil 4.0 g (85% or 3.4 g/d PUFA) and marine fish oil 440 mg), divided in doses with meals Control: large capsules of 1 g Ca Dose aim: increase ~3.5 g/d PUFA, 1.6% E PUFA Baseline PUFA unclear Compliance by biomarkers: neither biomarkers nor TC data reported Compliance by dietary intake: not reported Energy intake: not reported Total fat intake: not reported SFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake: not reported CHO intake: not reported CHO intake: not reported Alcohol intake: not reported Compliance, other methods: assessed by counting returned capsules at each visit, reported compliance > 90% Inclusion basis: no intention to increase total PUFA, planned dose ~3.5 g/d PUFA, 1. 6% E PUFA, > 10% higher than assumed 6% E from total PUFA at baseline PUFA dose: 1.6% E PUFA Length of intervention: 12 months	
Outcomes	Main trial outcome: BMD Dropouts: 23% (unclear by arm) Available outcomes: weight Response to contact: not attempted	
Notes	Trial funding: Scotia Pharmaceuticals Plc, Guildford, UK Mortality reported (1 death but unclear in which arm)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomized by staff at Scotia Pharmaceuticals Plc"
Allocation concealment (selection bias)	Unclear risk	No details

Bassey 2000-Post (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated but no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors were blinded for the BMD measurements but unclear for other outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	23% were lost to follow-up, unclear by arm and not all were accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record
Attention bias	Low risk	No difference was noted for intervention/ control groups
Compliance	Unclear risk	Neither biomarkers nor TC data reported
Other bias	Low risk	None noted

Bassey 2000-Pre

Methods	RCT, (high PUFA GLA+DHA+EPA vs low PUFA, both with Ca), 12 months Summary risk of bias: moderate or high
Participants	Healthy pre-menopausal women N: 19 intervention, 24 control (total randomised 64) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (SD): 34 (4.4) intervention, 35 (4.9) control Age range: 25-40 years (inclusion) Smokers: 0% intervention, 0% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported (Women on confounding drug therapy were excluded) Location: UK Ethinicty: not reported
Interventions	Type: capsules Comparsion: evening primrose oil + fish oil vs nil Intervention 10 large capsules/d of efacal (Ca 1.0 g, evening primrose oil 4.0 g and marine fish oil 440 mg), divided in doses with meals Control: large capsules of 1 g Ca Dose aim: increase ~3.5 g/d PUFA, 1.6% E PUFA Baseline PUFA unclear Compliance by biomarkers: neither biomarkers nor TC data reported

Bassey 2000-Pre (Continued)

	Compliance by dietary intake: not reported • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Protein intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported • Intake: not reported • Alcohol intake: not reported • PUFA dose: 1.6% E PUFA Length of intervention: 12 months	
Outcomes	Main trial outcome: BMD Dropouts: 31% (unclear by arm) Available outcomes: weight Response to contact: not attempted	
Notes	Trial funding: Scotia Pharmaceuticals Plc, Guildford, UK	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomized by staff at Scotia Pharmaceuticals Plc"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated but no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors were blinded for the BMD measurements but unclear for other outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	31% were lost to follow-up, unclear by arm and not all were accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record

Bassey 2000-Pre (Continued)

Attention bias	Low risk	No difference was noted for intervention/control groups
Compliance	Unclear risk	Neither biomarkers nor TC data reported
Other bias	Low risk	None noted

Bates 1977

Bates 1977	
Methods	RCT, parallel, 4 arms (n6 GLA+LA vs MUFA), 2 years Summary risk of bias: moderate to high
Participants	People with chronic progressive multiple sclerosis CVD risk: low N; intervention A, C: 38 per arm; control B, D: 38 per arm Mean years in trial: 2 % male: unclear (no statistically significant difference between groups) Age: unclear (no statistically significant difference between groups) Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK Ethenicty: not reported
Interventions	Type: supplement Comparison: GLA + linoleic (n6) vs oleic (MUFA) Intervention aims A: increase PUFAs with addition of 8 x 0.6 mL/d of Naudicelle oil in capsules (360 mg/d GLA plus 3.42 g/d linoleic acid plus < 1% ALA) Control aims B: increase MUFAs with addition of 8 x 0.6 mL/d of oleic acid in capsules (4.8 g oleic acid/d) A vs B dose aim: increase 0.34 g/d GLA, 3.78 g/d or 34 kcal or 1.7% E n-6 Intervention aims C: increase linoleic acid with addition of 11.5 g/d in a spread Control aims D: increase oleic acid with addition of 4 g/d in a spread C vs D dose aim: increase 11.5 g/d or 104 kcal or 5% E n-6 Baseline PUFA: unclear Compliance by biomarkers: unclear, no serum TC reported, no tissue fatty acids reported Compliance by dietary intake assessment: unclear, not reported Energy intake: not reported Total fat intake: not reported PUFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported Trans fat intake: not reported

Bates 1977 (Continued)

	 MUFA intake: not reported CHO intake: not reported Sugars intake: not reported Protein intake: not reported Alcohol intake: not reported Compliance, other methods: not reported Inclusion basis: aimed to increase total PUFA intake PUFA dose: A vs B 1.7% E PUFA, C vs D 5% E PUFA Duration of intervention: 2 years
Outcomes	Main trial outcome: progression or regression of multiple sclerosis Dropouts: unclear in all arms (deaths and dropouts reported together) Available outcomes: multiple sclerosis progression (deaths occurred but reported with dropouts, so numbers and arms unclear) Response to contact: yes, Professor Bates stated that data on mortality are no longer available
Notes	Trial funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Deaths and dropouts combined, no reasons for dropping out provided
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	Low risk	Capsules and spreads provided to all participants, no suggestion of attention bias
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported

Bates 1977 (Continued)

Other bias	Low risk	None found	
Bates 1978			
Methods	n6 LA vs MUFA using sup	RCT, parallel, 2 arms (n6 GLA+LA vs MUFA), using supplements (further 2 arms of n6 LA vs MUFA using supplementary foods not included as no outcome data), 2 years Summary risk of bias: moderate to high	
Participants	Mean years in trial: 2 % male: intervention A 34. 37.93% Age (SD) years: interventio D 33 (5) Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by ≥ 50 Medications taken by 20%-	g multiple sclerosis er arm; control B, D: 29 per arm 48%; intervention C 17.24%; control B 34.48%; control D In A 35 (9); intervention C 34 (8); control B 32 (7); control 10% of those in the control group: not reported 1-49% of those in the control group: not reported 25; but < 20% of the control group: not reported	
Interventions	Control aims B: 8 x capsules A vs B dose aim: increase (Intervention aims C: linole Control aims D: oleic acid C vs D dose aim: increase Baseline PUFA: unclear Compliance by biomarker "estimations of total fatty a showed that the percentage	audicelle capsules/d, 2.92 g/d LA plus 0.34 g/d GLA es/d (4 g/d oleic acid), 4 g/d MUFA 0.34 g/d GLA, 3.26 g/d or 29 kcal or 1.5% E n-6 ic acid spread (23 g/d linoleic acid) spread (16 g/d oleic acid) 23 g/d LA or 207 kcal or 10.4% E n-6 rs: good for C vs D, poor for A vs B, no serum TC reported acids in patients before and after 12-24 months' treatment of linoleic and arachidonic acids increased significantly only linoleic acid spread (group C)" take: unclear, not reported borted eported ereported	

Bates 1978 (Continued)

	 Sugars intake: not reported Protein intake: not reported Alcohol intake: not reported Compliance, other methods: not reported Inclusion basis: aimed to increase PUFA intake, but C vs D had no outcome data so was excluded PUFA dose: A vs B 1.5% E PUFA, C vs D 10.4% E PUFA (assumed from omega-6 doses) Duration of intervention: 2 years
Outcomes	Main trial outcome: progression or regression of multiple sclerosis Dropouts: A 0, B 1, C 3, D 6 Available outcomes: multiple sclerosis progression, deaths (nil in arms A, C and D) Response to contact: contact with Dr Bates
Notes	Trial funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly allocated"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Fairly well described, from 0-6 dropouts per arm over 2 years (each 29 randomised)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	Low risk	Appears equivalent
Compliance	High risk	No serum TC reported. Paper reports Quote: "estimations of total fatty acids in patients before and after 12-24 months' treatment showed that the percentage of linoleic and arachidonic acids increased sig- nificantly only in those patients taking the linoleic acid spread (group C)"

Bates 1978 (Continued)

		Only A vs B had outcomes for this review, data suggests poor compliance in this group
Other bias	Low risk	None found
Bates 1989		
Methods	RCT, parallel, (n3 EPA + D) Summary risk of bias: mode	
Participants	Level of risk for CVD: low Male: 34.2% intervention, 3 Mean age (SD): 34.0 (6.6) i. Age range: not reported but Smokers: not reported Hypertension: not reported	ontrol (analysed, int: 145 cont: 147) 30.6% control intervention, 33.7 (6.3) control 16-45 years inclusion criteria % of those in the control group: not reported 49%: not reported
Interventions	71 g/d EPA + 1.14 g/d DHA and ensure plentiful omega-Control: 20 x 0.5 g/d capsule fat and ensure plentiful ome ppm dodecylgallate to minin Dose aim : intervention incunclear. Control assumed to + DHA, dose 1.3% E PUFA Baseline PUFA not reported	rs MUFA capsules MaxEPA fish body oil (10 g/d fish oil providing 1. A + 10 IU/d vitamin E), plus all advised to reduce animal fat 66 fats. EPA + DHA 2.85 g/d es olive oil (10 g/d olive oil), plus all advised to reduce animal ega-6 fats. All capsules contained 0.5 IU vitamin E and 100 mise peroxide formation crease 2.85 g/d EPA + DHA, 1.3% E n-3, omega-6 dose have similar PUFA content to intervention, apart from EPA A es: adding serum EPA, DHA, LA and AA intervention 51. PUFA. TC not reported assessment: not reported orted ported ed orted reported reported reported orted orted orted orted orted orted orted

Bates 1989 (Continued)

	Sugars intake: not reported
	 Protein intake: intervention 1.07 g/kg/d (0.10), control 1.10 g/kg/d (0.07)
	Alcohol intake: not reported
	Compliance, other measures: not reported
	Inclusion basis: intended doses suggested total PUFA intake 1.3% E higher in inter-
	vention than control > 10% more than assumed 6% E PUFA at baseline
	PUFA dose: 1.3% E
	Duration of intervention: 24 months (5 years mentioned but outcomes not reported)
Outcomes	Main trial outcome: multiple sclerosis progress
	Dropouts: 10 intervention, 10 control
	Available outcomes: all-cause mortality, progress of multiple sclerosis, rate of multiple
	sclerosis relapse
	Response to contact: yes (no data provided)
	response to contact. yes (no data provided)
	Till for line Multiple Colonia Colonia of Control Dainia and North and London
Notes	Trial fillioning, Millitiple Acietosis Acciety of Catear Dritain and Northern Iteland bill
Notes	Trial funding: Multiple Sclerosis Society of Great Britain and Northern Ireland but Marfleet Refining provided fish oil and placebo capsules

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states research was "double blind" and control capsules Quote: "had the same appearance and flavour as the fish oil capsules and were packed and dispensed in identical fashion"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk at reported time points
Selective reporting (reporting bias)	High risk	No protocol or trials registration entries found. Trial was intended to run for 5 years, but outcomes only appear to be reported for the first 2 years
Attention bias	Low risk	Unlikely as each had capsules

Bates 1989 (Continued)

Compliance	Low risk	Adding serum EPA, DHA, LA and AA intervention 51.5% PUFA, control 47.6% PUFA. TC not reported
Other bias	Low risk	Not noted

Black 1994	
Methods	RCT, parallel, (low fat diet vs usual diet), 24 months Summary risk of bias: moderate or high
Participants	People with non-melanoma skin cancer N: 66 intervention, 67 control (analysed, 57 int, 58 cont) Level of risk for CVD: low Male: 54% intervention, 67% control Mean age (SD): 50.6 (9.7) intervention, 52.3 (13.2) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: white 100% (excluded from trial if of Asian, Black, Hispanic or American Indian ancestry)
Interventions	Type: dietary advice Comparison: reduced fat (lower omega-6 and total PUFA) vs usual diet Intervention: aims total fat 20% E, protein 15% E, CHO 65% E; methods 8 x weekly classes plus monthly follow-up sessions, with behavioural techniques being taught following individual approach (not clear if in a group or individual). 4-month intervals clinic examination by dermatologist. Intervention delivered face to face by a dietitian Control: aims usual diet; methods no dietary change, 4-month intervals clinic examination by dermatologist Dose aim: reduce total fat to 20% E, 15% E protein, 65% E CHO, particularly complex CHO (fat reduction included reducing omega-6 and total PUFA, no aim provided) Baseline PUFA 8% E Compliance by biomarkers: unclear, no serum TC reported, no tissue fatty acids Compliance by dietary intake: all assessed "during study", months 4-24, using 7-day food records verified by a dietitian • Energy intake, kcal/d: control 2196 (SD 615), intervention 1995 (SD 564) • Total fat intake, % E: control 37.8 (SD 4.1), intervention 20.7 (SD 5.5) (MD - 17.10, 95% CI -18.88 to -15.320 significant reduction • SFA intake, % E: control 12.8 (SD 2.0), intervention 6.6 (SD 1.8), (MD -6.20, 95% CI -6.90 to -5.50) significant reduction • PUFA intake, % E: control 7.8 (SD 1.4), intervention 4.5 (SD 1.3), (MD -3.30, 95% CI -3.79 to -2.81) significant reduction • PUFA n-3 intake: not reported

Black 1994 (Continued)

	 PUFA n-6 intake: LA, Control 16.9 (SD 5.6) g, intervention 8.5 (SD 3.3) g Trans fat intake: not reported MUFA intake, % E: control 14.4 (SD 1.7), intervention 7.6 (SD 2.2), (MD -6. 80, 95% CI -7.52 to -6.08) significant reduction CHO intake, % E: control 44.6 (SD 6.9), intervention 60.3 (SD 6.3), (MD 15. 70, 95% CI 13.29 to 18.11) significant increase Sugars intake: not reported Protein intake, % E: control 15.7 (SD 2.4), intervention 17.7 (SD 2.2), (MD 2. 00, 95% CI 1.16 to 2.84) significant increase Alcohol intake, % E: control 3.2 (SD 3.9), intervention 3.2 (SD 3.4) Inclusion basis: dietary intake data suggested total PUFA intake 3.3% E higher in control than intervention PUFA dose: -3.3% E Duration of intervention: 24 months (mean 1.9 years in trial)
Outcomes	Main trial outcome: incidence of actinic keratosis and non-melanoma skin cancer Dropouts: unclear intervention, unclear control Available outcomes: deaths, CVD deaths, cancer deaths (none), (weight data provided but without variance) Response to contact: Prof Black provided data on mortality
Notes	Trial funding: National Cancer Institute NOTE : for this trial the higher PUFA arm is the control, and lower PUFA arm is the intervention

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice provided, so participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"examined by dermatologists unaware of their treatment assignments". Deaths (all-cause and CVD) not considered rele- vant to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	For mortality. Unclear for other outcomes
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found

Black 1994 (Continued)

Attention bias	High risk	Weekly classes and monthly follow-up in intervention group, 4-monthly check-ups only in control	
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported	
Other bias	Low risk	None noted	
Brox 2001			
Methods	oil vs nil), 14 months	RCT, parallel, 3 arms (n3 EPA + DHA from cod liver oil vs n3 EPA + DHA from seal oil vs nil), 14 months Summary risk of bias: moderate or high	
Participants	N: 40 seal oil (SO), 40 cod lir Level of risk for CVD: moder Male: 53% seal oil, 50% cod Mean age, SD: 53.2 seal oil, 5 Age range: 43-66 Smokers: unclear Hypertension: unclear Medications taken by ≥ 50% Medications taken by 20%-49	Smokers: unclear Hypertension: unclear Medications taken by $\geq 50\%$ of those in the control group: none allowed Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Norway	
Interventions	Intervention: intervention: se n-3 3.9 g/d, total PUFA 4.2 g Cod liver oil, 15 mL/d (3.3 g PUFA 4.35 g/d): EPA + DH/d Control: nil, no supplement PUFA dose seal oil aim: (int E PUFA PUFA dose cod liver oil aim 2.0% E PUFA Baseline PUFA unclear Compliance by biomarkers: 2.4 (seal oil), 2.1 (cod liver oil was 10.3 mmol/L seal oil, 9. reported in intervention arms	Type: supplement (oil) Comparison: EPA + DHA vs nil Intervention: intervention: seal oil, 15 mL/d (2.6 g, 1.1 g/d EPA + 1.5 g/d DHA) (total n-3 3.9 g/d, total PUFA 4.2 g/d): EPA + DHA 2.6 g/d Cod liver oil, 15 mL/d (3.3 g, 1.5 g/d EPA + 1.8 g/d DHA) (total n-3 4.1 g/d, total PUFA 4.35 g/d): EPA + DHA 3.3 g/d Control: nil, no supplement PUFA dose seal oil aim: (intended) increase 2.6 g/d EPA + DHA, 1.2% E n-3, 1.9% E PUFA PUFA dose cod liver oil aim: (intended) increase 3.3 g/d EPA + DHA, 1.5% E n-3, 2.0% E PUFA Baseline PUFA unclear Compliance by biomarkers: serum omega-3 fatty acids, rose from around 1 mmol/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmol/L (control). Latest total PUFA in serum was 10.3 mmol/L seal oil, 9.9 mmol/L cod liver oil, 7.3 mmol/L control. Serum TC reported in intervention arms but not control, fell from 8.2 mmol/L at baseline to 7.8 mmol/L at 14 months in seal oil, 8.3 to 8.0 in cod liver oil (further data provided by trial authors)	

Brox 2001 (Continued)

Outcomes	 PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake: not reported CHO intake: not reported Sugars intake: not reported Protein intake: not reported Alcohol intake: not reported Alcohol intake: not reported Compliance, other measures: no other data Inclusion basis: intended dose appeared to be 1.9% or 2.0% increase in intervention arms compared to control, > 10% greater intake than the assumed 6% E from PUFA at baseline. Supported by serum fatty acid composition being higher in both intervention arms at 14 months than the control arm PUFA dose: 1.9% E SO, 2.0% E CLO Length of intervention: 14 months Main trial outcome: serum lipids Dropouts: 8 seal oil, 2 cod liver oil, 1 control Available outcomes: total and CV deaths, MI, combined CV events, TC, TG and HDL, adverse events (no stroke or SCD occurred, weight reported but too different at baseline and only reported to 6 months, data also provided by trial authors on apolipoproteins A1 and B, and Lp(a), but not used) Response to contact: yes (trial author provided methodological details and outcome data) Data of 2 intervention groups combined for dichotomous outcomes and cod liver oil vs 	
Pi-L-Cli	Trial funding: the trial was supported by the program Medical Research in Finnmark County, University of Tromsø	
Risk of bias Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	LOW IISK	J Brox stated (personal communication, January 2017) Quote: "The randomisation of the 120 participants was done by first generating 3 groups (seal oil, cod liver oil, control), then

giving each participant a number (1-120), putting all the numbers into the same hat and blindly drawing one number at the time from the hat. The first 40 numbers (1-40) were allocated to the seal oil group, the next 40 numbers (41-80) to the cod liver oil group and the rest (81-120) were allo-

Brox 2001 (Continued)

		cated to the control group."
Allocation concealment (selection bias)	Low risk	J Brox stated (personal communication, January 2017) Quote: "The researcher/clinician who in- vited the participants had no knowledge of to which group the participants would be allocated"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "controls were aware - not given a supplement"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	J Brox stated (personal communication, 2003) Quote: "All the persons involved in the drawing & analysing of blood were unaware of treatment. The technicians analysing the blood did not have any personal contact with the participants except K. Olaussen who did the FA analysis she only had access to the sample numbers not names and code. The participants did not know their number" [says elsewhere that K Olaussen did not know allocations]. "The only assessor was J Brox who did not have any personal contact with the participants, had nothing to do with the randomising or analysing process, or the collecting of results."
Incomplete outcome data (attrition bias) All outcomes	High risk	Seal oil group 10 dropouts, cod liver oil 3 dropouts, control group 3 dropouts. So substantial differences in rates of dropouts between the groups
Selective reporting (reporting bias)	Unclear risk	No trial protocol or trials register entry was found.
Attention bias	Low risk	No suggestion of differential attention
Compliance	Low risk	Latest total PUFA in serum was 10.3 mmol/L seal oil, 9.9 mmol/L cod liver oil, 7.3 mmol/L control. Serum TC reported in intervention arms but not control
Other bias	Low risk	No further bias noted

DART fat 1989

Methods	Diet And Reinfarction Trial (DART) RCT, 2 x 2 x 2 factorial (n6 LA vs mixed fats), also increased fish and increased fibre arms, 2 years Summary risk of bias: moderate to high
Participants	Men recovering from an MI CVD risk: high N: intervention: randomised 1018, analysed unclear; control: randomised 1015, analysed unclear Mean years in trial: control 1.9, randomised 1.9 % male: 100% Age: mean control 56.8, intervention 56.4 years Age range: all < 70 years Smokers: control 62.7%, intervention 61.2% Hypertension: intervention 24%, control 23.3% Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: beta-blockers, other anti-hypertensives, anti-anginals Medications taken by some, but < 20% of the control group: anti-coagulant, aspirin, other anti-platelet, digoxin, other cardiac drugs Location: UK Ethenicty: not reported
Interventions	Type: dietary advice Comparison: polyunsaturated oil and margarines (n6) vs usual dietary fats (SFA) Intervention aims: reduce fat intake to 30% E, increase polyunsaturated to saturated ratio (P/S) to 1.0 (using polyunsaturated oils and margarines), weight-reducing advice if BMI > 30 (dietitians provided the participants and their wives with initial individual advice and a diet information sheet, participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months) Control aims: no dietary advice on fat, weight-reducing advice if BMI > 30 (dietitians provided 'sensible eating' advice without specific information on fats) Dose aim: unclear Baseline n-6: unclear, but control PUFA intake 6.8% E Compliance by biomarkers: good, serum TC significantly reduced in intervention compared to control (-0.26 mmol/L, 95% CI -0.37 to -0.15) Compliance by dietary intake: assessed using a 7-day weighted food diary, of a 25% random subsample • Energy intake, MJ/d: intervention 7.3 (SD 1.8), control 7.7 (SD 1.9) • Total fat intake, % E: intervention 31 (SD 7), control 35 (SD 6) • SFA intake: intervention 11% E (SD 3), control 15% E (SD 3), dose -4% E • PUFA intake: intervention 9.4% E, control 6.6% E, dose +2.8% E (most of which omega-6) • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • PUFA of 6.8% E • Trans fat intake: not reported

DART fat 1989 (Continued)

	 CHO intake: intervention 46% E (SD 7), control 44% E (SD 6) Sugars intake: not reported Protein intake: % E: intervention 18 (SD 4), control 17 (SD 4) Alcohol intake: intervention 5% E (SD 6), control 4% E (SD 6) Compliance, other measures: no other data Inclusion basis: intended to increase PUFA/SFA ratio, as well as reduce total fat. TC was lower in intervention than control, and intake data suggest PUFA intake higher by 2.8% E in intervention than control, > 10% greater than baseline of 6.8% E PUFA dose: 2.8% E Duration of intervention: 2 years
Outcomes	Main trial outcomes: mortality, reinfarction Dropouts: all followed for events regardless of compliance (ITT) Available outcomes: CV events (CV deaths plus non-fatal MI), cancer deaths, total MI, non-fatal MI, TC, HDL Response to contact: yes, Professor Burr provided additional data and information on methodology
Notes	Note: this was a 2 x 2 x 2 factorial trial, and so some in each group were randomised to increased fatty fish and/or increased cereal fibre Trial funding: Welsh Scheme for Development of Health and Social Research, Welsh Heart Research Foundation, Flora Project (commercial), Health Promotion Research Trust

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "outcome assessors were not aware of study allocation" (Prof Burr, personal communication) Method of blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	GPs contacted for information on mortality and morbidity when participants did not attend, data collected from mortality register
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located

DART fat 1989 (Continued)

Attention bias	High risk	Those given dietary advice almost certainly given more time and attention than those in the control group (with no dietary advice)
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.26 mmol/L, 95% CI -0.37 to -0.15)
Other bias	Low risk	None found

DIPP-Tokudome 2015

DIPP-Tokudome 2015		
Methods	Dietary Intervention for Patients Polypectomized for tumours of the colorectum (DIPP) RCT, parallel, 2 arms (n3 EPA + DHA + ALA vs nil), 24 months Summary risk of bias: moderate or high	
Participants	Poeple previously polypectomised for colorectal tumours N: 104 intervention, 101 control Level of risk for CVD: low Male: 73.1% intervention, 74.3% control Mean age (SD): 58.3 (9.5) intervention, 59.7 (8.9) control Age range: 35-75 Smokers: 65.4% intervention, 61.4% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: supplements Medications taken by 20%-49% of those in the control group: none Medications taken by some, but < 20% of the control group: oral contraceptive pills Location: Japan Ethnicity: not reported	
Interventions	Type: advice plus supplement (fish oil capsules) Comparison: n3 EPA + DHA + ALA vs nil Intervention: advice to reduce total fat intake, decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from fish/marine foods, increase intake of n-3 PUFAs from perilla oil rich in ALA, and take 8 capsules of fish oil/day (equivalent to 96 mg/day of EPA and 360 mg/day of DHA) Control: advice to decrease intake of fats/oils as a whole Dose aim: increase 0.46 g/d EPA + DHA plus EPA + DHA from fish plus ALA from perilla, unclearn3, unclear PUFA Baseline PUFA: unclear but control 6.3% E PUFA Compliance by biomarkers: plasma fatty acid concentrations, fatty acid compositions in the membranes of red blood cells and the sigmoid colon. Plasma fatty acids suggested higher total PUFA intakes in intervention group (at 24 months 4.91 mmol/L, SD 1.23 in intervention group, 4.59 mmol/L, SD 0.76 in control). But TC higher in intervention (5.52 mmol/L, SD 0.9) than control (5.40 mmol/L, SD 0.79) at 24 months Compliance by dietary intake: assessed using semi-quantitative food frequency questionnaire • Energy intake, kcal/d: intervention 2268 (SD 535), control 2131 (SD 563)	

	 Total fat intake, g/1000 kcal: intervention 28.4 (SD 5.1), control 28.07 (SD 6.27) SFA intake, g/1000 kcal: intervention 7.02 (SD 1.74), control 7.27 (SD 2.03) PUFA intake, % E: intervention 7.4, control 6.3 PUFA n-3 intake, g/1000 kcal: intervention 3.24 (SD 1.15), control 1.49 (SD 0.39) PUFA n-6 intake, g/1000 kcal: intervention 4.38 (SD 1.01), control 4.90 (SD 1.46) Trans fat intake: not reported MUFA intake, g/1000 kcal: intervention 9.07 (SD 2.05), control 10.09 (SD 2.67) CHO intake, g/1000 kcal: intervention 129.5 (SD 15.8), control 133.96 (SD 17.98) Sugars intake: not reported Protein intake, g/1000 kcal: intervention 39.0 (SD 5.6), control 36.6 (SD 5.72) Alcohol intake: not reported Compliance, other measures: none Inclusion basis: no intention to increase total PUFA. Intention was to increase omega-3 but dose unclear. Total PUFA intakes were higher in intervention than control by 1. 1%E, > 10% more than control PUFA dose: 1.1% E Length of intervention: 24 months
Outcomes	Main trial outcome: number and size of colorectal tumours Dropouts: 3 intervention, 5 control Available outcomes: all-cause mortality, dietary intake, plasma fatty acids, lipids, side effects, glucose Response to contact: yes (methodological details provided)
Notes	Trial funding: all were either government or charity grants.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated using random digit number for allocation of participants
Allocation concealment (selection bias)	Low risk	Trial author confirmed "Allocation information was blinded to clinicians and researchers" but no methodology provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	From the 2015 paper, "The attending physicians as well as the participants were blinded to the assignment information". However in the discussion section they say "complete participant blinding could not have been achieved because free-living participants might have exchanged information on their dietary intervention, say in the hospital waiting room"

DIPP-Tokudome 2015 (Continued)

		Trial author confirmed blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "physicians, including colono- scopists, a scientist who conducted blood and specimen analyses, and pathologists were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All those randomised were accounted for.
Selective reporting (reporting bias)	High risk	The researchers chose not to report data on the number, size and pathological type of the colorectal tumours as they said they would in the trials register. They reported more outcomes in the paper than initially stated. UMIN000000461 Registered 03 August 2006, recruitment completed 01 March 2007
Attention bias	Low risk	Participants were given equal follow-up.
Compliance	Unclear risk	Plasma fatty acids suggested higher total PUFA intakes in intervention group (at 24 months 4.91 mmol/L, SD 1.23 in intervention group, 4.59 mmol/L, SD 0.76 in control). But TC higher in intervention (5. 52 mmol/L, SD 0.9) than control (5.40 mmol/L, SD 0.79) at 24 months
Other bias	Low risk	None noted

Dodin 2005

Methods	RCT, parallel, (n3 ALA vs n6 LA), 12 months Summary risk of bias: moderate or high
Participants	Healthy menopausal women N: 101 intervention, 98 control (analysed, intervention: 85 control: 94) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (SD): 54.0 (4.0) intervention, 55.4 (4.5) control Age range: 49-65 Smokers: 8% intervention, 6% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Canada Ethnicity: French Canadian

Interventions	Type: food supplement (flaxseed) Comparison: more ALA vs less ALA Less representations (0 old flavored in compared into dieta (providing 21 071 o total lignores)
	Intervention: 40 g/d flaxseed incorporated into diets (providing 21,071 g total lignans, 180 calories, 16 g lipids (57% ALA), and 11 g total dietary fibre): 9.1 g/d ALA
	Control: 40 g/d wheat germ incorporated into diets (providing 196 g total lignans, 144 calories, 4 g lipids (6.9% ALA), and 6 g total dietary fibre: 0.26 g/d PUFA
	Dose aim: increase 8.8 g/d PUFA, 4.0% E PUFA
	Baseline PUFA 5.4% E
	Compliance by biomarkers: plasma fatty acid total PUFA (summing LA, GLA, AA,
	EPA, DHA, DPA, ALA) increased 3.02% from baseline to 12 months in control, increased 1.99% in intervention
	Compliance by dietary intake: assessed by 3-day food diary at baseline and 12 months
	• Energy intake, kcal/d: intervention 1878, change -36 SD 413, control baseline 2021, change -138, SD 461
	 Total fat intake, change % E: intervention +1.4 (SD 6.5), control -1.4 (SD 7.7) SFA intake, change % E: intervention -0.3 (SD 3.5), control -0.5 (SD 3.9)
	 PUFA intake, change % E: intervention +2.4 (SD 2.0), control +0.9 (SD 2.2) PUFA n-3 intake: not reported
	PUFA n-6 intake: not reported
	Trans fat intake: not reported
	• MUFA intake, change % E: intervention -0.3 (SD 3.6), control -1.4 (SD 4.2)
	• CHO intake, change % E: intervention -0.9 (SD 5.5), control +2.5 (SD 7.4)
	Sugars intake: not reported O(E): O(E
	 Protein intake, change % E: intervention -0.2 (SD 3.0), control -0.4 (SD 3.1) Alcohol intake, change % E: intervention -0.3 (SD 3.5), control -0.7 (SD 4.1)
	Compliance, other methods: first morning urine collection was performed at randomi-
	sation and at month 12 to measure urinary lignin levels. In addition, trial participants recorded their daily intake of seeds on diary cards and were asked to return unused bread
	and packages of seeds at each visit. Good compliance reported
	Inclusion basis: no intention to increase total PUFA, planned dose -4.0% E PUFA,
	dietary intake data suggested 1.5% E PUFA, biomarkers suggested greater PUFA intake in control, TC rose in control and fell in intervention. Using dietary intake dose of 1. 5% E PUFA higher in intervention, > 10% higher than 5.6% E from total PUFA at
	baseline
	PUFA dose: 1.5% E PUFA Duration of intervention: 12 months
Outcomes	Main trial outcome: BMD
	Dropouts: 26 intervention, 17 control (but 13/17 had an endpoint evaluation)
	Available outcomes: weight, BMI, QoL, BP, lipids, glucose, adverse events, dietary intake,
	plasma fatty acids Response to contact: yes, trial author confirmed that no CV events or deaths occurred
	during the trial
Notes	Trial authors replied to tell us that there were no deaths or CV events during the trial Trial funding: not reported
Risk of bias	

Dodin 2005 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule was prepared by the clinical unit of the research centre using computer-generated randomisation in blocks of 4-8
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the trial Quote: "a local baker prepared loaves of bread. Each week, the loaves of bread were delivered in sealed, opaque unmarked wrappers to the Department of Food and Nutrition Sciences at Laval University. The seeds were ground up and vacuum-packed in the same laboratory. The Department of Food and Nutrition Sciences was responsible for labelling the bags of bread and packages of seeds with the subject's randomization number. Bread and packages of seeds were provided on a 3-month basis. The foods that both groups received was similar in appearance and packaging and was kept frozen until consumption to avoid essential fatty acid."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT. Loss to follow-up 10%, reasons given.
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trials registry entry found
Attention bias	Low risk	All participants had same number of visits
Compliance	High risk	Plasma fatty acid total PUFA (summing LA, GLA, AA, EPA, DHA, DPA, ALA) increased 3.02% from baseline to 12 months in control, increased 1.99% in intervention
Other bias	Low risk	None noted

Doi 2014

Methods	RCT, parallel, (n3 EPA vs nil, both with statins), 12 months Summary risk of bias: moderate or high
Participants	Patients having PCI after acute MI N: 119 intervention, 119 control analysed Level of risk for CVD: high Male: 77% intervention, 76% control Mean age (SD): 70 (11) intervention, 71 (12) control Age range: unclear Smokers: 28% intervention, 32% control Hypertension: 71% intervention, 69% control Medications taken by ≥ 50% of those in the control group: aspirin, ticlopidine, β- blockers, statins (as part of treatment) Medications taken by 20%-49% of those in the control group: ARB/ ACE inhibitors Medications taken by some, but < 20% of the control group: none Location: Japan Ethnicity: not reported
Interventions	Type: supplement (EPA) Comparison: EPA vs nil Intervention: purified EPA ethyl esters (> 98%) 1.8 g/d EPA within 24 h after PCI plus statins Control: statins with no EPA Dose aim: increase 1.8 g/d EPA + DHA, 0.8% E n-3, 0.8 %E PUFA Baseline PUFA: unclear Compliance by biomarkers: plasma EPA reported at 6-8 months, higher in intervention (162.8 mg/L) than control (65.5 mg/L). No further biomarker or TC data reported Energy intake: not reported Energy intake: not reported Total fat intake: not reported SFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported PUFA n-6 intake: not reported MUFA intake: not reported CHO intake: not reported Alcohol intake: not reported Alcohol intake: not reported Alcohol intake: not reported Inclusion basis: no intention to increase total PUFA. Intention was to increase omega-3 by 0.8% E. Total PUFA appear to be 0.8% E higher in intervention, > 10% more than assumed 6% E baseline PUFA dose: 0.8% E Length of intervention: 12 months
Outcomes	Main trial outcome: CV events Dropouts: 1 intervention, 2 control Available outcomes: mortality, stroke, MI, sudden death, CV death, revascularisation

Doi 2014 (Continued)

	Response to contact: contact attempted but no response to date		
Notes	Trial funding: trial registry states "self-funded". The trial authors received honoraria from Mochida Pharmaceutical Co		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation plan, which included stratification by age and sex	
Allocation concealment (selection bias)	Unclear risk	Carried out by research technician but unclear	
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label but blind endpoint	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data on outcomes were collected from clinical charts. Unclear if blinded. Diagnoses were confirmed by investigator blind to treatment allocation	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 dropouts, similar rates between the groups and reasons given	
Selective reporting (reporting bias)	High risk	Data collection completed before trial registry entry. Only 1% dropout	
Attention bias	Low risk	Timing of follow-ups similar	
Compliance	Unclear risk	Plasma EPA reported at 6-8 months, higher in intervention (162.8 mg/L) than control (65.5 mg/L). No further biomarker or TC data reported	
Other bias	Low risk	None observed	
Dullaart 1992			
Methods	RCT, parallel, 2 arms (n6 LA vs mixed fats), 2 years Summary risk of bias: moderate to high		
Participants	People with type I diabetes with elevated urinary albumin CVD risk: moderate Intervention: randomised 18, analysed 16 Control: randomised 20, analysed 20		

Dullaart 1992 (Continued)

% male: 81% intervention, 75% control

Age: mean (SD) intervention 44 (12), control 41 (14)

Age range: unclear (21-65 inclusion)

Smokers: intervention 50%, control 55%

Hypertension: intervention 6%, control 10%

Medications taken by ≥ 50% of those in the control group: insulin

Medications taken by 20%-49% of those in the control group: not reported

Medications taken by some, but < 20% of the control group: anti-hypertensives

Location: Netherlands Ethnicty: not reported

Interventions

Type: dietary advice

Comparison: LA (n6) vs usual diet

Intervention: diet advice given at every visit throughout the 2-year period to increase linoleic acid achieving a polyunsaturated: saturated fatty acid ratio close to 1.0. Advice to replace butter or saturated margarines by polyunsaturated margarines and to restrict the intake of SFA from meat and milk products

Control: to continue their usual diet. All participants were urged not to alter total fat and protein content

Dose: aim unclear

Baseline PUFA: 6.6% E PUFA

Compliance: TC fell more in intervention (-0.45 mmol/L) than control (0.10 mmol/L) from baseline to 2 years. Significant difference between plasma cholesteryl ester LA in intervention and control at 2 years

Plasma cholesteryl esters at 2 years

- LA mol%: intervention 62.2 (SD 4.2), control 57.4 (SD 4.9)
- oleic acid mol%: intervention13.7 (SD 1.8), control 16.5 (SD 1.4)

Dietary assessment using 1 week dietary recall, reported at 2 years.

- Energy intake, MJ/d: intervention 7.42 (SD 2.02), control 8.48 (SD 2.48)
- Total fat intake, % E: intervention 37 (SD 4), control 40 (SD 7)
- SFA intake, % E: intervention 13 (SD 2), control 16 (SD 3)
- PUFA intake, % E: (calculated from P/S and SFA intake) intervention 12.5 (SD not reported), control 9.0 (SD not reported), increase 3.5%E
 - PUFA n-3 intake: not reported
- $\bullet\,$ PUFA n-6 intake, % E: not reported, but intervention 11%E LA (SD 2), control 7%E LA (SD 3)
 - PUFA/SFA ratio: intervention 0.96 (SD 0.16), control 0.56 (SD 0.25)
 - MUFA intake: not reported
 - CHO intake, % E: intervention 43 (SD 4), control 41 (SD 7)
 - Protein intake, % E: intervention 18 (SD 4), control 17 (SD 3)
 - Trans fat intake: not reported
 - Cholesterol intake, mg/d: intervention 174 (SD 49), control 245 (SD 120)

Compliance, other methods: not reported

Inclusion basis: aimed to increase LA rather than total PUFA intake. Intake data suggests 3.5% E PUFA dose, > 10% increase from control 9% E intake Supported by plasma cholesteryl ester LA and TC

PUFA dose: 3.5% E PUFA
Duration of intervention: 2 years

Dullaart 1992 (Continued)

Outcomes	Main trial outcomes: albuminuria and lipids Dropouts: intervention 2 of 20, control 4 of 20 Available outcomes: weight, HDL, TGs, HbA1c (TC, glucose, insulin reported but too different at baseline to use, LDL not reported in control group, renal outcomes such as glomerular filtration rate, albuminuria, mean arterial pressure not used) Response to contact: yes, trial author confirmed no MI or other CVD events occurred during trial
Notes	Most outcomes are estimated from figures. Trial funding: Dutch Diabetes Research Fund

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were stratified according to sex and randomised in blocks of ten men and six women"
Allocation concealment (selection bias)	Low risk	Assigned using opaque sealed envelopes by independent statistical investigator with no contact with participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding. Participants could not be blinded as they received dietary advice
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details on dropouts apart from the exclusion of 2 intervention participants from the trial due to pregnancy and decision not to participate
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration located
Attention bias	High risk	Likely that diet-advice group had more time and attention
Compliance	Low risk	TC fell more in intervention (-0.45 mmol/L) than control (0.10 mmol/L) from baseline to 2 years. Significant difference between plasma cholesteryl ester LA in intervention and control at 2 years
Other bias	Low risk	None noted

EPIC-1 2008

Methods	EPANOVA in Crohn's disease, trial 1 (EPIC-1) RCT, parallel, 2 arms (n3 EPA + DHA vs mixed fats), 52 weeks Summary risk of bias: moderate or high
Participants	Adults with quiescent Crohn's Disease Activity Index score < 150 N: 188 intervention, 186 control Level of risk for CVD: low Male: 48.1% intervention, 41.1% control Mean age (SD): 40.5 (15.2) intervention, 38.2 (13.1) control Age range: 18-70 years Smokers: 30.6% intervention, 34.4% control Hypertension: unclear Medications taken by ≥ 50% of those in the control group: oral 5-ASA therapy, systemic corticosteroids - prednisolone, budesonide Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: antibiotic therapy, topical rectal therapy, immune-modifying agents, immune modifiers/biologics Location: Canada, Europe, Israel, USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MCT Intervention: 2 x 2 1 g gelatine capsules omega-3-free fatty acids (Epanova- 2.2 g EPA, 0.8 g DHA) Control: 4 x1 g capsules medium-chain triglycerides Dose aim: increase 3.0 g/d EPA + DHA, 1.4% E n-3, 1.4% E PUFA Baseline PUFA: unclear Compliance by biomarkers: not reported, neither fatty acids nor TC Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • Trans fat intake: not reported • CHO intake, % E: not reported • Protein intake, % E: not reported • Protein intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported Compliance, other measures: pill counts, 79.2% adhered intervention, 75.6% adhered control Inclusion basis: no intention to increase total PUFA. Intention was to increase 3.0 g/d EPA + DHA, 1.4% E n-3, 1.4% E PUFA, > 10% greater than assumed baseline of 6% E. PUFA dose: 1.4% E Length of intervention: mean 52 weeks

EPIC-1 2008 (Continued)

Outcomes	Main trial outcome: Crohns relapse-free time Dropouts: 80 intervention, 91 control Available outcomes: total deaths, non-fatal arrhythmias, cancer diagnoses, cancer deaths, adverse events Response to contact: yes (data provided)	
Notes	Trial funding: Tillotts Pharma, trial authors had extensive financial disclosures	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by number generator. Used a centralised randomisation procedure via interactive voice-recognition system
Allocation concealment (selection bias)	Low risk	Centralised randomisation (see above)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding stated, identical capsule (slow-release capsules). Neither investigator nor participant knew the allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial states double-blind but does not state that outcome assessors were blinded or pro- vide a mechanism for this
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of dropouts and reasons provided. 171 of 187 in intervention group and 174 of 184 in control group provided data for primary outcome, (7% dropout), though 80 in the intervention group and 91 in the control group terminated early
Selective reporting (reporting bias)	High risk	Trials registration (NCT00613197) first received in 2008, but trial started in 2003, and was published in 2008
Attention bias	Low risk	As investigators were blinded attention bias was not possible
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Low risk	No further bias noted

EPIC-2 2008

Methods	EPANOVA in Crohn's disease, trial 2 (EPIC-2) RCT, parallel, 2 arms (n3 EPA + DHA vs mixed fats), 58 weeks Summary risk of bias: moderate or high
Participants	Adults with a confirmed diagnosis of Crohn's disease and a Crohn's Disease Activity Index score < 150 who are responding to steroid induction therapy N: intervention, 189, control 190 (187 intervention, 188 control analysed) Level of risk for CVD: low (people with quiescent Crohn's disease) Male: 48.1% intervention, 41.1% control Mean age (SD): 38.5 (13.8) intervention, 40.0 (13.6) years control Age range: > 16 years Smokers: 25.1% intervention, 37.2% control Hypertension: unclear Medications taken by ≥ 50% of those in the control group: systemic corticosteroids - prednisolone, budesonide (but tapered and discontinued during the trial) Medications taken by 20%-49% of those in the control group: only reported for prior 12 months Medications taken by some, but < 20% of the control group: only reported for prior 12 months Location: Canada, Europe, Israel, USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MCT Intervention: 2 x 2 1 g gelatine capsules omega-3-free fatty acids (Epanova) providing total dose -2.2 g/d EPA, 0.8 g/d DHA: EPA + DHA -3.0 g/d Control: 2 x 2 1 g capsules medium-chain triglyceride oil Dose aim: increase 3.0 g/d EPA + DHA, 1.4% E n-3, 1.4% E PUFA Baseline PUFA: unclear Compliance by biomarkers: not reported, neither fatty acids nor TC Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • Sugars intake: not reported • CHO intake, % E: not reported • CHO intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported Inclusion basis: no intention to increase total PUFA. Intention was to increase 3.0 g/d EPA + DHA, 1.4% E n-3, 1.4% E PUFA, > 10% greater than assumed baseline of 6% E PUFA dose: 1.4% E

EPIC-2 2008 (Continued)

Other bias

	Length of intervention: mean 58 weeks	
Outcomes	Main trial outcome: maintain Crohns symptomatic remission Dropouts: 114 intervention, 112 control Available outcomes: mortality, CV events (nil), cancer diagnoses, adverse events Response to contact: yes (data provided)	
Notes	Trial funding: Tillotts Pharma, trial authors had extensive financial disclosures	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by number generator. Used a centralised randomisation procedure via interactive voice-recognition system
Allocation concealment (selection bias)	Low risk	Centralised randomisation (see above)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinding stated, identical capsule (slow-release capsules). Neither investigator nor participant knew the allocation. However no information provided on capsules taste or smell
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial states double-blind but does not state that outcome assessors were blinded or pro- vide a mechanism for this
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of dropouts and reasons provided, however 114 of 189 in intervention group and 112 of 190 in control group terminated early
Selective reporting (reporting bias)	High risk	NCT00074542. First received 2003, trial start 2002. Published 2008. Some outcomes, such as quality of life, stated in trials registry but not in published papers
Attention bias	Low risk	As investigators were blinded attention bias was not possible
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
0.1.1:		27.6.1.1.

Low risk

No further bias noted

EPOCH 2011

Methods	Older People, Omega-3 and Cognitive Health (EPOCH) RCT, parallel (n3 EPA + DHA vs MUFA), 18 months Summary risk of bias: low
Participants	Healthy older adults with no cognitive impairment N: 195 intervention, 196 control (reported by trial author) Level of risk for CVD: low Male: not reported Mean age (SD): not reported Age range: not reported, but 65-90 recruited Smokers: not reported Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: supplement (fish oil capsules) Comparison: high EPA + DHA vs MUFA and low EPA + DHA Intervention: 4 capsules/d (1.72 g/d DHA and 0.60 g/d EPA): EPA + DHA 2.32 g/d Control: 4 capsules/d (3.960 g/d olive oil and 40 mg/d fish oil), 0.8 g/d PUFA (assuming 20% of olive oil is PUFA) Dose aim: increase 2.28 g/d EPA + DHA, or 1.52 g/d PUFA (subtracting control data) , 0.68% E PUFA Baseline PUFA unclear Compliance by biomarkers: erythrocyte membrane n-3 LC PUFA status assessed but no useful data reported, no TC data Compliance by dietary intake: not reported Energy intake: not reported Total fat intake: not reported FUFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported MUFA intake: not reported Trans fat intake: not reported CHO intake: not reported CHO intake: not reported Alcohol intake: not reported Alcohol intake: not reported Alcohol intake: not reported Alcohol intake: not reported Compliance, other methods: count of all unused supplements returned at 3-monthly intervals, plus self-report calendars, mailed back on a monthly basis. If compliance fell below 85% (re calendars), they were contacted by a researcher who noted the reasons Inclusion basis: no intention to increase total PUFA intake. Dose aim 1.52 g/d PUFA or 0.68% E total PUFA, > 10% increase from assumed 6% E PUFA baseline. No data on biomarkers, intake or TC PUFA dose: 0.68% E Length of intervention: 18 months

EPOCH 2011 (Continued)

Outcomes	Main trial outcome: change in cognitive performance Dropouts: not reported Available outcomes: mortality (nil), MI, stroke, revascularisation, atrial fibrillation, CV events. Planned outcomes, not reported in publications, included: cognitive outcomes, functional outcomes, glucose, lipids, plasma fatty acids, BP, inflammation and oxidative stress Response to contact: yes (data provided)
Notes	Trial authors reported some events, but don't appear to be published Trial funding: EPAX donated the Omega-3 concentrate and Blackmores Pty Ltd donated the placebo and packaging of the Omega-3 concentrate. The trial was supported by the Brailsford Robertson Award 2007-2008 (University of Adelaide and CSIRO Food and Nutritional Sciences), and is funded by a National Health and Medical Research Project Grant (#578800)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Age-stratified, permuted-block randomisation, with mixed block-sizes (2-8, size unknown to trial investigators), 1:1 allocation. Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	An independent researcher prepared allocation to treatment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The researchers, project staff, and participants remained blinded to treatment allocation until the trial was completed and the database locked. No information provided on capsules' appearance, taste or smell, but fish oil added to control to make taste similar
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data for each group presented, and no attrition data presented
Selective reporting (reporting bias)	High risk	Registered at ACTRN12607000278437. Only cognitive functions reported for whole population (not by arm). No secondary outcomes reported (Mini Mental State Examination; perceived health status, depressive symptoms, positive and negative

EPOCH 2011 (Continued)

		affect, life satisfaction, self-reported cognitive functioning, and functional capacity; BP; biomarkers of glucose, glycated haemoglobin, TGs, TC, HDL, LDL, homocysteine, CRP, Malondialdehyde (MDA), and telomere length)
Attention bias	Low risk	All had the same contact and attention
Compliance	Unclear risk	Compliance assessed by erythrocyte membrane n-3 long-chain PUFA status but results not reported, no TC or biomarker data on total PUFA
Other bias	Low risk	None noted

FAAT - Leaf 2005

Methods	Fatty Acid Antiarrhythmia Trial - FAAT Randomisation: RCT, parallel, 2 arms, (n3 EPA + DHA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with implanted cardioverter defibrillators (ICDs) N: intervention 200, control 202 Level of risk for CVD: high (participants with ICDs). Male: intervention 84.5%, control 81.7% Mean age (SD): intervention 65.7 (11.6), control 65.3 (11.7) years Age range: unclear Smokers: intervention 15%, control 11.4% Hypertension: unclear Medications taken by ≥ 50% of those in the control group: ACEi, beta-blockers Medications taken by 20%-49%: diuretics Medications taken by some, but < 20%: Ca channel blockers, amiodarone, sotalol, type 1 antiarrhythmics Location: USA Ethnicity: intervention 95.5% white, control 96.5% white
Interventions	Type: supplement/capsule Comparison: EPA + DHA vs MUFA Intervention: 4 x 1 g/d fish oil gelatin capsules, 2.6 g EPA + DHA/d (Pronova Biocare, quantities of EPA + DHA unclear): EPA + DHA 2.6 g/d Control: 4 x 1 g/d olive oil capsules, 4 g/d (in identical gelatin capsules, < 0.06 g/d EPA + < 0.06 g/d DHA) All were advised to use olive oil rather than the common plant seed oils for cooking, dressings, and sauces PUFA Dose: (intended) Dose aim: intervention 2.6 g/d EPA + DHA, 1.2% E n3, 1.2% E PUFA, control 4 g olive oil, 20% LA, 0.8 g/d PUFA, 0.36% E PUFA. Difference 0.84% E PUFA Baseline PUFA: unclear

	Compliance by biomarkers: platelet phospholipid EPA + DHA higher in intervention		
	group than control, no data on total PUFA or TC		
	Compliance by dietary intake: not reported		
	Energy intake: not reported		
	Total fat intake: not reported		
	SFA intake: not reported		
	 PUFA intake: not reported PUFA n-3 intake: not reported 		
	PUFA n-6 intake: not reported		
	Trans fat intake: not reported		
	MUFA intake: not reported		
	CHO intake: not reported		
	Sugars intake: not reported		
	Protein intake: not reported		
	Alcohol intake: not reported		
	Compliance, other measures: pill counts suggested greater omega-3 intake in interven-		
	tion participants. 35% were non-compliers (36.5% intervention, 34.2% control)		
	Inclusion basis: no intention to increase total PUFA. Intention was to increase omega-		
	3, difference between arms was 0.84% E PUFA, > 10% more than control		
	PUFA dose: 0.84% E		
	Duration of intervention: 12 months		
0	Main trial outcome: fatal VF/VT		
Outcomes			
	Dropouts: intervention 13 deaths, unclear number of dropouts; control 12 deaths, drop-		
	outs unclear		
	Available outcomes: deaths, CV deaths, deaths from heart failure, fatal arrhythmias, MI,		
	angina		
	Response to contact: yes (data provided)		
Notes	Trial funding: the trial was supported in part by a grant from the NHLBI, NIH		
	(HL62154)		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation tables for each collaborating site, stratified by site
Allocation concealment (selection bias)	Low risk	Trial author confirmed allocation was concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial referred to as "double blind" and gelatin capsules (verum and placebo) were stated as being of identical appearance but no discussion of taste or smell. Trial author confirmed that investigators and participants were blinded

FAAT - Leaf 2005 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	VT and VF events were assessed blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Large numbers dropped out so some deaths etc. may have been missed, 35% discontinued early due to non-compliance but were assessed at trial end, data censored for some participants
Selective reporting (reporting bias)	High risk	Trials registry data received September 2005, paper published November 2005
Attention bias	Low risk	Time and attention appeared similar between the 2 arms
Compliance	High risk	Platelet phospholipid EPA + DHA higher in intervention group than control, no data on total PUFA or TC
Other bias	Low risk	None noted

GLAMT 1993

Methods	Gamma Linolenic Acid Multicentre Trial (GLAMT) RCT, 2-arm, parallel (n6 GLA vs non-fat), 1 year Summary risk of bias: moderate to high
Participants	People with mild diabetic neuropathy CVD risk: moderate Control: randomised 57, analysed 48 (with ≥ 1 evaluation) Intervention: randomised 54, analysed 52 Mean years in trial: control 1.0, randomised 1.0 % male: intervention 67%, control 79%, Age, mean (SD) years: intervention 53.3 (11.1), control 52.9 (11.4) Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by ≥ 50% of those in the control group: insulin Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK and Finland Ethenicty: not reported
Interventions	Type: supplement Comparison: GLA (n-6) vs placebo (paraffin) Control aims: 12 capsules/d paraffin Intervention aims: 12 capsules/d evening primrose oil (EP4, equivalent to Epogam): 0.

48 g/d GLA plus LA (stated as the major constituent, dose reapsule then 8.4 g/d*) Dose aim: increase 0.48 g/d GLA or 4 kcal or 0.2% E GLA 76 kcal or 3.8% E LA, total 4% E n6 Baseline PUFA: unclear Compliance by biomarkers: unclear, no serum TC or tissue Compliance by dietary intake: unclear Energy intake: not reported Total fat intake: not reported SFA intake: not reported PUFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake: not reported MUFA intake: not reported CHO intake: not reported		al or 0.2% E GLA, increase ~8.4 g/d LA or	
	 Sugars intake: not reported Protein intake: not reported Alcohol intake: not reported Compliance, other methods: not reported Inclusion basis: aimed to increase GLA intake rather than total PUFA. Dose aim appeared to be ~4% E PUFA (from omega-6 data), >10% more than assumed baseline of 6% E PUFA. No confirmatory biomarker or intake data PUFA dose: 4% E PUFA (estimated from aim) Duration of intervention: 1 year 		
Outcomes	Main trial outcome: measures of diabetic neuropathy Dropouts: intervention 10, control 17 Available outcomes: MI, cancer (no deaths) Response to contact: contact attempted but no response to date		
Notes	Trial funding: Scotia Pharmaceuticals		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Not described	
Allocation concealment (selection bias)	Unclear risk	Not described	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, and Quote: "Active and placebo capsules were indistinguishable in taste or appearance"	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, though trial described as double- blind no methods or statement of blinding of outcome assessors was mentioned	

GLAMT 1993 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for withdrawal usually given, but high and dissimilar
Selective reporting (reporting bias)	Unclear risk	No clear protocol or trials registry entry found
Attention bias	Low risk	Appeared similar
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Low risk	None identified

HARP- Sacks 1995

HAICE - Sacks 1999	
Methods	Harvard Atherosclerosis Reversibility Project (HARP) RCT, (n3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	People with coronary heart disease N: 41 intervention, 39 control (99.9% follow-up at trial end) Level of risk for CVD: high Male: 93.5% intervention, 92.9 % control Mean age (SD): 62 (7) intervention, 62 (7) years control Age range: 30-75 Smokers: 0% (exclusion criteria) Hypertension: 48% intervention, 36% control Medications taken by ≥ 50% of those in the control group: beta blockers, antiplatelet agents Medications taken by 20%-49% of those in the control group: Ca channel blockers, nitrates Medications taken by some, but < 20% of the control group: ACE inhibitors, oral hypoglycaemic drugs Location: USA Ethenicity: not reported
Interventions	Type: supplement (capsule) Comparison: n3 vs MUFA Intervention: 12 fish oil capsules/d (Promega, Parke-Davis) in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 PUFAs composed of EPA (240 mg), DHA (160 mg) and other (100 mg) (mainly DPA) providing total daily dose of 6 g/d of n-3 fatty acids. Control: olive oil capsules identical in appearance to the fish oil capsules, 6 g/d olive oil, 1.2 g/d LA Dose aim: increase 4.8 g/d PUFA, 2.2% E PUFA Baseline PUFA: unclear Compliance by biomarkers: adipose fatty acids (sum of LCn3 fats, AA & LA) were 21. 2% in intervention group, 20.4% in control group. TC was slightly higher in intervention

	(5.02 mmol/L, SD 0.96) than control (4.99 mmol/L, SD 0.62) at 28 months Compliance by dietary intake: not reported. • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Protein intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported Tinclusion basis: no intention to increase total PUFA. Intention was to increase omega-3, difference between arms was 4.8 g/d PUFA, 2.2% E PUFA, > 10% increase from assumed baseline of 6% E PUFA PUFA dose: 2.2% E PUFA Duration of intervention: average 28 months		
Outcomes	Main trial outcome: regression of coronary artery lesions Dropouts: 10 intervention, 11 control Available outcomes: total and CV deaths, fatal and non-fatal MI, stroke, angioplasty or coronary artery bypass graft, unstable angina, CHD, cancer diagnosis, combined CV events, side effects Response to contact: yes		
Notes	Trial funding: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, Bethesda, Maryland, Warner Lambert-Parke Davis (pharmaceutical company), East Hanover, New Jersey; and by an Established Investigator Award to Dr. Sacks from the American Heart Association, Dallas, Texas		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	"randomization" stratified by clinical management regime and TC/HDL ratio	
Allocation concealment (selection bias)	Unclear risk	No further details	
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheteriza- tion, and analysis of angiography films were blinded to the treatment assignment" Although capsules were identical in appear- ance, no information on their taste and	

HARP- Sacks 1995 (Continued)

		smell
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheteriza- tion, and analysis of angiography films were blinded to the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate over 28 months and all reasons are well-documented
Selective reporting (reporting bias)	High risk	Trial registered retrospectively after publication
Attention bias	Low risk	Nothing in description implies the arms were treated differently
Compliance	Unclear risk	Adipose fatty acids (sum of LCn3 fats, AA & LA) were 21.2% in intervention group, 20.4% in control group. TC was slightly higher in intervention (5.02 mmol/L, SD 0.96) than control (4.99 mmol/L, SD 0.62) at 28 months
Other bias	Low risk	None noted

HERO-Tapsell 2009

Methods	Healthy Eating to Reduce Overweight in people with type 2 diabetes (HERO) RCT, parallel, (n3 ALA vs low n3), 12 months Summary risk of bias: moderate or high
Participants	Overweight adults with non-insulin treated diabetes N: 26 intervention, 24 control (analysed, int: 18 cont: 17) Level of risk for CVD: moderate Male %: not reported Mean age (SD): 54 (8.7), not reported by arm Age range: 33-70 Smokers: not reported Hypertension: not reported Medications taken by \geq 50% of those in the control group: lipid-lowering drugs, oral hypoglycemics Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: food supplement (walnuts) Comparison: ALA vs nil Intervention: 30 g/d snack portions of walnuts, aim 30% E fat (10% SFA, 10% MUFA,

	oil supplements, ALA dose unclear Control: no supplements, aim 30% E fat (1) protein, 50% E CHO Both groups were given low-fat isocaloric did 3 times/week Dose aim: increase 5% E PUFA Baseline PUFA: unclear but control 5.5% F Compliance by biomarkers: omega-3 fat acid levels which were similar in both gro 0.3 mmol/L from baseline to 12 months intervention Compliance by dietary intake: all assesses interview and 3-day food records • Energy intake, kcal/d: intervention 19 • Total fat intake, % E: control 29.3 (SI • PUFA intake, % E: intervention 8.1 (SI • PUFA intake, % E: control 5.5 (SD 2.3.2), • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: intervention 10.9 • CHO intake, % E: intervention 41.4 • Sugars intake: not reported • Protein intake, % E: intervention 21.1 • Alcohol intake, % E: not reported Compliance, other measures: not reported Inclusion basis: no intention to increase to which included increasing PUFA in place of	s measured by erythrocyte membrane fatty ups, no other PUFAs reported. TC fell by in control, and fell by 0.1 mmol/L in the d at 12 months using validated diet history 14 (SD 443), control 2112 (SD 685) D 7.2), int ervention34.1 (SD 5.8) D 2.6) 3), intervention 12.0 (SD 2.5)cont 9.6 (SD 0 (SD 3.0), control 11.2 (SD 2.8) (SD 6.2), control 42.3 (SD 7.6)
Outcomes	Main trial outcome: change in body weight and % body fat Dropouts: 8 intervention, 5 control Available outcomes: all-cause mortality (nil deaths), weight, visceral adipose tissue, lipids, glucose, insulin, HbA1c (body fat % and subcutaneous adipose tissue measured but too different at baseline to use) Response to contact: not yet attempted	
Notes	Body fat % was too different between groups at baseline hence data not used Trial funding: California Walnuts Commission	
Risk of bias		
Bias	Authors' judgement	Support for judgement

HERO-Tapsell 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Randomisation was conducted using a computerised random-number generator by a researcher independent of the subject interface
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Subjects, but not dietitians, were blinded to the type of overall diet (a prepackaged 30 g snack portion of walnuts was given to the walnut group unbeknown to the controls)" However, there was no placebo supplement so blinding not truly feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "code was concealed from the researchers collecting data, as well as from subjects." However as participants could not be blinded outcome assessors may not have been (problem for measures of adiposity, not for biochemical measures)
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate, 35 of 50 analysed (30% attrition rate)
Selective reporting (reporting bias)	Unclear risk	Trial was registered but post-analysis
Attention bias	Low risk	Both groups appear to have had same level of attention
Compliance	High risk	Omega-3 fats measured by erythrocyte membrane fatty acid levels which were similar in both groups, no other PUFAs reported. TC fell by 0.3 mmol/L from baseline to 12 months in control, and fell by 0. 1 mmol/L in the intervention
Other bias	Low risk	None noted

Houtsmuller 1979

Methods	RCT, parallel, (increase LA vs usual diet), 72 months maximum Summary risk of bias: moderate or high
Participants	Adults with newly diagnosed diabetes N: 51 intervention, 51 control (analysed unclear intervention, unclear control) Level of risk for CVD: moderate

Houtsmuller 1979 (Continued)

	Male: 56% overall (not stated by intervention arm) Mean age (SD): not reported intervention, not reported control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by \geq 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: statins (probably) Location: Netherlands Ethenicity: not reported
Interventions	Type: dietary advice Comparison: omega-6 vs SFA and CHO Intervention: aims total fat 40% E, 1/3 LA, CHO 45% E, protein 15% E; methods unclear, surveyed by dietitian. Intervention appears to have been delivered by dietitian but no details on format or frequency Control: aims SFA 35% E, CHO 50% E, protein 15% E; methods unclear, surveyed by dietitian Dose aims: increase ~9% E LA (aims imply no LA in control, but paper states LA was 4 x higher in intervention than control, est 3% E control, 12% E int, so increase of ~9% E) Baseline PUFA: unclear Compliance by biomarkers: good, serum TC significantly reduced in intervention compared to control (-0.47 mmol/L, 95% CI -0.76 to -0.18), no significant differences in men, but significant improvements in women from 3 years Compliance by dietary intake: unclear (not reported) • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA intake: not reported • CHO intake: not reported • Alcohol intake: not reported • Protein intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported Compliance, other measures: not reported Inclusion basis: aimed to increase LA, not total PUFA. Appears to have increased LA by ~9% E so assume increase in total PUFA also ~9% E, > 10% increase from control group baseline of ~3% E from PUFA PUFA dose: 9% E PUFA Duration of intervention: 72 months
Outcomes	Main trial outcome: progression of diabetic retinopathy Dropouts: unclear intervention, unclear control Available outcomes: CV events (total MI and angina), TC, TGs (data read off graph), CHD mortality (fatal MI), CHD events (MI, angina), progression of retinopathy

Houtsmuller 1979 (Continued)

	Response to contact: contact attempted but no response to date	
Notes	Trial funding: Dutch Heart Foundation	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants matched in pairs then ran- domised
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear, though unlikely as dietary advice provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention bias	Unclear risk	No details provided
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.47 mmol/L, 95% CI -0.76 to -0.18)
Other bias	High risk	Some concerns around fraud in the first author's later research on diet in cancer. No allegations found regarding his research in diabetes (but much information is in Dutch)
Kumar 2012		
Methods	RCT, parallel, (n3 EPA + DHA vs nil), 12 months Summary risk of bias: moderate or high	
Participants	People with persistent AF on warfarin N: 92 intervention, 90 control (91 and 87 analysed ITT) Level of risk for CVD: high Male %: 82.4 intervention, 72.4 control	

Kumar 2012 (Continued)

Kumai 2012 (Commun)	
	Mean age (SD): 63 (10) intervention, 61 (13) control Age range: 18-85 (inclusion criteria) Smokers: 22.2% intervention, 11.5% control Hypertension: 45.6% intervention, 58.6% control Medications taken by \geq 50% of those in the control group: anti-arrhythmic drugs, reninangiotensin system inhibitors Medications taken by 20%-49% of those in the control group: statins Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: fish oil capsule Comparison: EPA + DHA vs nil Intervention: 6 capsules/d of a fish oil preparation containing a total dose of 1.02 g of EPA and 0.72 g DHA. Participants in the omega-3 group were asked to continue fish oils till a maximum of 1 year or till return of persistent AF Control: no supplements. Participants were advised not to take any fish oil supplements All participants underwent cardioversion following randomisation Dose aim: increase 1.74 g/d EPA + DHA, 0.8% E n-3, 0.8% E PUFA Baseline PUFA: unclear Compliance by biomarkers: phospholipid fatty acid status measured at cardioversion, DHA and EPA higher in intervention (EPA 2.5% fat, DHA 6.3% fat) than control (EPA 1.2% fat, DHA 3.4% fat), both P < 0.001. No other PUFAs, or TC, reported Compliance by dietary intake: not reported Energy intake, kcal/d: not reported Energy intake, kcal/d: not reported SFA intake, %E: not reported SFA intake, %E: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported PUFA n-6 intake: not reported CHO intake, % E: not reported Protein intake, % E: not reported Alcohol intake, % E: not reported Compliance, where measures: monitored on a weekly basis via telephone and during follow-up by using a pill count, results not reported Inclusion basis: no intention to increase total PUFA. Intention was to increase 1.74 g/d EPA + DHA, 0.8% E PUFA > 10% greater than assumed baseline of 6% E. No biomarker, TC or intake data to confirm PUFA dose: 0.8% E Duration of intervention: 1 year (or AF recurrence)
Outcomes	Main trial outcome: AF recurrence Dropouts: 4 intervention, 0 control Available outcomes: all-cause mortality (nil death), AF recurrence, time to AF recurrence, adverse events Response to contact: written but no answer yet

Kumar 2012 (Continued)

Notes	Trial funding: the trial was funded in part by the National Heart Foundation of Australia and the Pfizer Cardiovascular Lipid Research Grant		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to a control or an omega-3 group in a 1:1 fashion (no methodological details)	
Allocation concealment (selection bias)	Unclear risk	No further details	
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label with no placebo control	
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label	
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT conducted	
Selective reporting (reporting bias)	Unclear risk	Trial registered 2005 but data collection started 2003	
Attention bias	Unclear risk	Intervention group had capsules, while control group did not. Potential for greater contact and checking with intervention group, otherwise groups seem to have had the same care	
Compliance	Unclear risk	Phospholipid fatty acid status measured at cardioversion, DHA and EPA higher in intervention (EPA 2.5% fat, DHA 6.3% fat) than control (EPA 1.2% fat, DHA 3.4% fat), both P < 0.001. No other PUFAs, or TC, reported	
Other bias	Low risk	None noted	

Kumar 2013

Methods	RCT, parallel, (n3 EPA + DHA vs nil), 12 months Summary risk of bias: moderate or high
Participants	Adults > 60 years with sinoatrial node disease and dual chamber pacemakers N: 39 intervention, 39 control (only 18 vs 39 for 12-month analyses) Level of risk for CVD: moderate/high Male %: 46% intervention, 56% control Mean age (SD): 78 (7) intervention, 77 (8) control Age range: not reported Smokers: not reported Hypertension: 72% Medications taken by ≥ 50% of those in the control group: statins, renin-angiotensin system inhibitors Medications taken by 20%-49% of those in the control group: anti-arrhythmic drugs Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: omega-3 capsule Comparison: EPA + DHA vs nil Intervention: a triglyceride preparation containing a total of 6 g/day of omega-3 PUFAs of which 1.8 g/day were n-3 (1.02 g EPA and 0.72 g DHA) Control: no supplements Dose aim: increase 1.74 g/d EPA + DHA, 0.8% E n-3, 0.8% E PUFA Baseline PUFA: unclear Compliance by biomarkers: phospholipid fatty acid status measured at randomisation and at 1-3 months, DHA and EPA increased in intervention, not in control. No other PUFAs, or TC, reported Compliance by dietary intake: measured via weekly diet history, but no results reported Energy intake, kcal/d: not reported Energy intake, % E: not reported FUFA intake, % E: not reported FUFA n-6 intake: not reported CHO intake, % E: not reported Fortein intake: not reported Alcohol intake, % E: not reported Fortein intake, % E: not reported Alcohol intake, % E: not reported Fortein intake, % E: not reported Alcohol intake, % E: not reported Fortein intake, % E: not reported Fortein intake, % E: not reported Alcohol intake, % E: not reported Fortein intake, % E: not reported Fortein intake, % E: not reported Alcohol intake, % E: not reported Fortein intake intak

Kumar 2013 (Continued)

Outcomes	Main trial outcome: AF burden Dropouts: 1 intervention, 0 control Available outcomes: all-cause mortality, CV mortality, AF (frequency and duration but not recurrence so not used), adverse events Response to contact: written, no reply to date	
Notes	Trial funding: unclear	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using sequentially numbered, opaque, sealed envelopes
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "At each visit, stored AT/AF diagnostic data were retrieved in an un-blinded fashion"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 1 lost, and reason explained. But group baseline size to cross-over is huge. Doesn't report just the 17 or 18 metrics at baseline, no idea why the 21 were the ones switched and mixed with the control
Selective reporting (reporting bias)	Low risk	Trial prospectively registered and outcomes stated were reported
Attention bias	Unclear risk	Only difference would be handing out the capsules, rest seems the same. However, one group is getting supplements and the other nil
Compliance	Unclear risk	Phospholipid fatty acid status measured at randomisation and at 1-3 months, DHA and EPA increased in intervention, not in control. No other PUFAs, or TC, reported
Other bias	High risk	21 of the 39 randomised to the intervention were crossed over to control at six months so 12-month outcomes are reported for 17/

	18 intervention group while baseline characteristics are reported for all 39 participants
Ley 2004	
Methods	RCT, parallel, (reduced total fat vs usual diet), 12 months Summary risk of bias: low (dietary advice trial)
Participants	Adults with impaired glucose intolerance or high normal blood glucose N: 85 intervention, 90 control (176 between both groups) (analysed 66 intervention: 70 control at 1 year, 112 between both groups at 5 years) Level of risk for CVD: moderate Male: 80% intervention, 68% control Mean age (SD): 52.5 (SE 0.8) intervention, 52.0 (SE 0.8) control Age range: not reported Smokers: 23% intervention, 9% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: BP medication taken by 27% intervention, 18% control Location: New Zealand Ethnicity: European 67% intervention, 77% control, Maori 11% intervention, 7% control, Pacific islander 20% intervention, 13% control, other 3% intervention, 4% control (outcomes not provided by ethnicity)
Interventions	Type: diet advice Comparison: reduced fat vs usual diet Intervention: aim reduced fat diet (no specific goal stated); methods monthly small group meetings to follow a 1-year structured programme aimed at reducing dietary fat, includes education, personal goal setting, self-monitoring Control: aim usual diet; methods usual intake plus general advice on healthy eating consistent with the New Zealand guidelines and standard dietary information for people with nutrition-related problems upon entering the trial Dose aim: no goal stated Baseline PUFA: unclear but lower PUFA arm 4% E PUFA Compliance by biomarkers: erythrocyte ALA increased by 28% in control, reduced by 17% in intervention (in a subsample of participants, % of total fatty acids in red blood cells also increased in control group compared to intervention), no other erythrocyte fatty acids reported. TC fell by 0.15 mmol/L (SE 0.09) in control, and by 0.05 mmol/L (SE 0.17) in intervention to 1 year Compliance by dietary intake: mean of five, 24-h diet recalls over 2 years of trial • Energy intake, kcal/d: intervention 1821 (SD not reported), control 1593 (SD not reported) • Total fat intake, % E: intervention 33.6 (SE 7.8), control 26.1 (SE 7.7) • SFA intake, %E: intervention 10.0 (SE 0.6), control 13.4 (SE 0.6) • PUFA intake, % E: intervention 4.0 (SE 0.2), control 4.8 (SE 0.2)

Ley 2004 (Continued)

	 PUFA n-3 intake: not reported PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake, % E: intervention 8.9 (SE 0.4), control 11.8 (SE 0.4) CHO intake, % E: intervention 54.2 (SE 1.5), control 45.8 (SE 1.4) Sugars intake: not reported Protein intake, % E: intervention 18.4 (SE 0.5), control 16.6 (SE 0.5) Alcohol intake, % E: intervention 3.6 (SE 1.0), control 5.7 (SE 0.9) Compliance, other methods: not reported Inclusion basis: aimed to reduce total fat, not to alter total PUFA. Resulted in fall of 0. 8% E total PUFA in intervention, > 10% increase from 5.3% E PUFA at baseline PUFA dose: 0.8% E PUFA (from dietary intake data) Duration of intervention: 12 months (later data reported, but intervention only lasted 1 year)
Outcomes	Main trial outcome: lipids, glucose, BP Dropouts: unclear intervention, unclear control Available outcomes: mortality, CVD mortality, combined CV events (including MI, angina, stroke, heart failure), diabetes diagnosis, total MI, stroke, cancer diagnoses, cancer deaths, CHD events (MI or angina), weight, total, LDL and HDL, TGs, BP Author contact: Dr Metcalf provided additional methodology and outcome data
Notes	Trial funding: National Heart Foundation of New Zealand, Aukland Medical Research Foundation, Lotteries Medical Board and the Health Research Council of New Zealand NOTE: total PUFA intake lower in intervention than control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter al- location later (trial author stated in their reply to us that randomisation and prepa- ration of the envelopes was by people not involved in recruitment)
Allocation concealment (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter al- location later
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice, not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial authors stated that those assessing lipids were blinded

Ley 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, trialists asked for data but they were unable to provide any - unclear if any data missing
Selective reporting (reporting bias)	Low risk	No protocol or trials registry entry found
Attention bias	High risk	Regular meetings in intervention group, not in control
Compliance	Low risk	Erythrocyte ALA increased by 28% in control, reduced by 17% in intervention (in a subsample of participants, % of total fatty acids in red blood cells also increased in control group compared to intervention), no other erythrocyte fatty acids reported. TC fell by 0.15 mmol/L (SE 0.09) in control (the arm higher in PUFA), and by 0.05 mmol/L (SE 0.17) in intervention to 1 year (control group should have been higher in total PUFA in this trial)
Other bias	Low risk	None noted

MARINA - Sanders 2011

Methods	Modulation of Atherosclerosis Risk by Increasing dose of N-3 fatty Acids (MARINA) RCT, parallel, 4 arms (n3 EPA + DHA at 3 doses vs MUFA), G2 vs control included, 12 months Summary risk of bias: low
Participants	Non-smoking men and women aged 45-70 years N: intervention 279 in 3 groups (G1 0.45 g/d N = 94, G2 0.9 g/d N = 93, G3 1.8 g/d N = 92), control: 88 (analysed G1 0.45 g/d N = 81, G2 0.9 g/d N = 80, G3 1.8 g/d N = 80, control 71) Level of risk for CVD: low Male: 38.7% intervention, 38.6% control Mean age (CI): G1:55 (53, 56), G2:55 (54, 56), G3: 55 (54, 57) intervention 55 (54, 57) control Age range: 45-70 Smokers: 0% intervention, 0% control Hypertension: 5.4% intervention, 5% control Medications taken by \geq 50% of those in the control group: none Medications taken by 20%-49% of those in the control group: none Medications taken by some, but < 20% of the control group: statins, antihypertensives, hormone replacement therapy, thyroxine Location: UK Ethnicity: G1: white 80.9%, black 4.3%, Asian 6.4%, Far Eastern 4.3%, other 4.3%

	G2: white 78.5%, black 6.5%, Asian 10.8%, Far Eastern 0%, other 4.3% G3: white 85.9%, black 1.1%, Asian 2.2%, Far Eastern 4.3%, other 6.5% Control: white 77.3%, black 10.2%, Asian 6.8%, Far Eastern 2.3%, other 3.4%
Interventions	Type: supplement (fish oil capsules) Comparison 1: EPA + DHA vs MUFA Comparison 2: high EPA + DHA vs low EPA + DHA Intervention: 3 x 1 g oil gelatin capsule/day consisting of blend of EPA concentrate, DHA concentrate, refined olive oil and 0.1 wt% peppermint oil Providing a daily dose of; 0.45 g, 0.9 g, or 1.8 g/d (all with EPA/DHA ratio of 1.51) Control: 3 gelatin capsules/d containing refined olive oil + 0.1% peppermint oil Dose aim: (intended) increase 0.45 g/d EPA + DHA, 0.2% E n-3 or increase 0.9 g/d EPA + DHA, 0.4% E n-3 or increase 1.8 g/d EPA + DHA, 0.8% E n-3 Baseline PUFA 6.2% E Compliance by biomarkers: EPA and DHA in erythrocyte lipids increased in dose-dependent manner compared with placebo, indicating long-term compliance with intervention. TC rose by 0.1 mmol/L in both the control and intervention (G2, 0.9 g/d group) from baseline to end. No other biomarkers reported Compliance by dietary intake: all assessed after treatment (assumed at 12 months), using food frequency questionnaire (checked for completeness). Intervention group refers to G2 (0.9 g/d): • Energy intake, MJ/d (95% CI): intervention 7.98 (7.28 to 8.68), control 7.79 (6. 92 to 8.67) • Total fat intake, % E (95% CI): intervention 34.0 (32.4 to 35.5), control 30.8 (28.9 to 32.6) • SFA intake, % E (95% CI): intervention 12.1 (11.5 to 12.8), control 11.1 (10.3 to 11.9) • PUFA n-3 intake: not reported • PUFA n-6 intake
Outcomes	Main trial outcome: endothelial function, arterial stiffness Dropouts: 38 intervention (13,13,12), 17 control Available outcomes (for G2 vs control used): lipids, dietary intake, CRP, BP (supine and

MARINA - Sanders 2011 (Continued)

	ambulatory - numeric data not provided, but trial states that there were no significant differences between arms). Weight data not used, as baseline is different between groups (FMD, arterials stiffness, carotid intima media thickness, heart rate variability, heart rate, endothelial progenitor cells reported but not used) Contact with authors: yes (many outcomes above provided in end of trial report from authors)
Notes	NOTE: outcome data used G2 (0.9 g/d EPA + DHA) vs placebo for continuous outcomes, as this was the comparison where dietary data suggested that total PUFA increased by > 10% compared with placebo Trial funding: Food Standards Agency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the random allocation sequence was generated with a computer program by using the process of minimisation to balance age, sex and ethnicity between treatment groups."
Allocation concealment (selection bias)	Low risk	Quote: "We enrolled eligible participants and the trial database program allocated a series of capsules to the participant"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "blends of the test fat with 0.1wt% peppermint oil to disguise the fish taste of the EPA and DHA" Peppermint oil in both intervention and control capsules.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatments associated with the capsule codes were concealed from all investigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database."
Incomplete outcome data (attrition bias) All outcomes	Low risk	15% withdrawal, reasons for attrition reported
Selective reporting (reporting bias)	Low risk	Outcomes published match trials register. Registered September 2008, trial started June 2008, ended December 2010, main publication 2011
Attention bias	Low risk	No difference between groups

MARINA - Sanders 2011 (Continued)

Compliance	High risk	EPA and DHA in erythrocyte lipids increased in dose-dependent manner compared with placebo, indicating long-term compliance with intervention. TC rose by 0.1 mmol/L in both the control and intervention (G2, 0.9 g/d group) from baseline to end. No other biomarkers reported
Other bias	Low risk	None noted

McIllmurray 1987

Methods	RCT, parallel, 2 arms (GLA vs "inert placebo"), 40 months Summary risk of bias: moderate to high
Participants	People within 1 month following operation to remove Dukes's C colorectal cancer N: intervention 25 (plus some dropouts), control: 24 (plus some dropouts (analysed intervention 25, control 24). 5 dropped out, but arms unclear Level of risk for CVD: low Male: not reported Mean age (SD) years: intervention 62.1 (not reported), control 64.8 (not reported) Age range: intervention 48-81, control 45-77 Smokers: not reported Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK Ethnicity: not reported
Interventions	Type: supplement (Efamol) Comparison: GLA vs "inert placebo" (unclear what) Intervention: 6 capsules/d containing 500 mg GLA plus 10 mg natural vitamin E (Efamol). GLA 0.5 g/d, 60 mg/d vitamin E. Plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine Control: 6 capsules/d containing an inert placebo, identical in appearance (not specified what). Plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine Dose aim: (assuming placebo contains no PUFA) increase 0.5 g/d GLA, 5 kcal or 0. 2% E GLA, assume 70% LA*, 4.2 g/d or 37.8 kcal/d or 1.9% E LA, 2.1% E n6 Baseline PUFA: unclear Compliance by biomarkers: unclear, no serum TC or tissue fatty acid levels reported. Compliance by dietary intake: unclear, states that one participant stopped taking the supplements at 12 months • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported

McIllmurray 1987 (Continued)

	 PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake: not reported CHO intake: not reported Sugars intake: not reported Protein intake: not reported Alcohol intake: not reported Alcohol intake: not reported Inclusion basis: aimed to increase GLA rather than total PUFA. Aimed to increase omega-6 by 2.1% E, assume 2.2% E increase for PUFA, > 10% of assumed 6% E PUFA baseline. No confirmatory biomarker, TC or intake data PUFA dose: 2.2% E PUFA Duration of intervention: 40 months 	
Outcomes	Main trial outcome: unclear, "survival", probably mortality Dropouts: 5 (unclear from which groups) Available outcomes: mortality, cancer mortality (face flushing reported as a side effect, but no numbers provided and assumed due to concomitant pyridoxine) Response to contact: Professor McIllmurray replied, "I don't have the recordsso I have nothing more than what appears in the publication. I do not recall there being any cardiovascular events."	
Notes	Trial funding: not stated, Efamol Ltd provided the Efamol capsules and inert capsules *EPO described as being ~70% LA in some publications, this and a 1 g capsule size have been assumed where no other details are provided	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details apart from the placebo was identical in appearance to the Efamol capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 dropouts, unclear from which arms
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found

McIllmurray 1987 (Continued)

Attention bias	Low risk	Supplement provided, no suggestion of attention bias
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Unclear risk	None noted, but contents of placebo capsules unclear

Mendis 2001

Methods	RCT, 2 arms, parallel (n6 LA vs non-fat) dietary advice, 1 year Summary risk of bias: moderate to high
Participants	Healthy volunteers responding to survey. Some had hyperlipidaemia. CVD risk: low N: 30 intervention, 30 control (analysed 26 intervention, 28 control) % male: 78% (total) Mean age: not reported Age range: 20-65 years Smokers: not reported Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported *lipid-lowering medications as well as many others were not allowed Location: Sri Lanka Ethnicty: 100% Sri Lanakan
Interventions	Type: diet advice plus test fat supplement Comparison: n-6 vs non-fat (unclear if CHO, protein or both) Intervention: group B received a diet containing 20% E as fat (4.7% coconut fat) plus 7. 5 g/d test fat containing soybean fat-sesame fat (3:1, v/v containing PUFA:MUFA ratio 2). Fat intake in group B was, therefore, 24% energy intake. (test fat provided additional 5 g/d PUFA mainly LA) Control: Group A received a diet containing 20% E as fat (4.7% E coconut fat) Dose aim: increase 5 g/d PUFA, 2.2% E PUFA Baseline PUFA: unclear Compliance by biomarkers: poor, serum TC was not significantly reduced in intervention compared to control (0.16 mmol/L, 95% CI -0.18 to 0.50). The intervention group were stated as having higher dietary PUFA:SFA ratio than controls, but no blood levels of fatty acids were reported Compliance by dietary intake: unclear, measured by field workers' visits and using food diaries • Energy intake, kJ/d: intervention 7962 (SD 1568), control 8030 (SD 1465) • Total fat intake, % E: intervention 24 (SD not reported), control 20 (SD not reported) • SFA intake % E: intervention 11.4 (SD not reported), control 11.8 (SD not

Allocation concealment (selection bias)

(performance bias)

All outcomes

bias) All outcomes

Blinding of participants and personnel High risk

Blinding of outcome assessment (detection Unclear risk

	 PUFA intake: not reported (unsaturated fat intake intervention 12.6% E, control 8.2% E, test fat reported as mainly LA) PUFA n-3 intake: not reported PUFA n-6 intake: (unsaturated fat intake intervention 12.6% E, control 8.2% E, test fat reported as mainly LA) Trans fat intake: not reported MUFA intake: not reported CHO intake, % E: intervention 64 (SD not reported), control 67 (SD not reported) Sugars intake: not reported Protein intake, % E: intervention 12.2 (SD not reported), control 12.1 (SD not reported) Alcohol intake: not reported Compliance, other methods: not reported Inclusion basis: did not aim to increase PUFA (but replace SFA with unsaturated fats) Did appear to increase unsaturated fat by 4.4% E, and test fat reported as mainly LA. Aim was to increase PUFA by 2.2% E, assume this achieved though no biomarker or dietary intake data and TC was not reduced in intervention PUFA dose: 2.2% E PUFA Duration of intervention: 1 year 	
Outcomes	Main trial outcome: serum lipids Dropouts: intervention 4, control 2 Available outcomes: lipids Response to contact: contact attempted but no response to date	
Notes	Trial funding: funded by the National Science Foundation of Sri Lanka	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to 2 groups (groups A and B). This was done in such a way that the 38 hyperlipidaemic participants were equally divided between the two groups.

Unclear risk

No details

No details

The groups had different diets with test fat

added to intervention group

Mendis 2001 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Six participants dropped out at 6 months but their data are not included in the analysis at all
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention bias	Low risk	Appeared similar
Compliance	High risk	TC was higher in intervention than control (0.16 mmol/L, 95% CI -0.18 to 0.50). The intervention group were stated as having higher dietary PUFA:SFA ratio than controls, but no blood levels of FAs were reported
Other bias	Unclear risk	No details provided on the form or method of supply of diet or test fat

Mita 2007

Methods	RCT, parallel, (n3 EPA vs nil), 2 years Summary risk of bias: moderate or high
Participants	Japanese people with type 2 diabetes N: intervention 40, control 41 (analysed 30, 30) Level of risk for CVD: moderate Male: 53% intervention, 67% control Mean age (SD): 59 (11.2) intervention 61.2 (8.4) control Age range: not reported Smokers: 40% intervention, 43% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: oral hypoglycemics Medications taken by 20%-49% of those in the control group: insulin, lipid-lowering drugs, antihypertensives Medications taken by some, but < 20% of the control group: antithrombotics Location: Japan Ethnicity: 100% Japanese
Interventions	Type: supplement (EPA oil capsules) Comparison: EPA vs nil Intervention: 1.8 g/d EPA as EPADEL capsules (Mochida Pharmaceutical Co Ltd Japan) 98% pure ethyl-ester EPA (unclear how many capsules) Control: no intervention Dose aim: increase 1.8 g/d EPA + DHA, 0.8% E n-3, assumed 0.8% E from total PUFA as no control Baseline PUFA not reported Compliance by biomarkers: no tissue fatty acids reported, but TC lower in intervention arm (5.37 mmol/L SD 0.74 at baseline, 5.15 mmol/L SD 0.83 at 2 years), than control

	(5.37 mmol/L SD 1.03 at baseline, 5.27 mmol/L SD 0.99 at 2 years) Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • Sugars intake: not reported • Sugars intake: not reported • Protein intake, % E: not reported • Alcohol intake, % E: not reported Compliance, other methods: checked during 3-month reviews throughout trial and 5 participants were excluded for poor compliance but no details on method or results Inclusion basis: planned dose suggested in increase in total PUFA (by 0.8% E, > 10% increase from an assumed baseline of 6% E), and higher PUFA in the intervention is backed up by TC data PUFA dose: 0.8% E Length of intervention: mean 2.1 (0.2) years	
Outcomes	Main trial outcome: progression of diabetic macroangiopathy measured by carotid intima-media thickness and brachial-ankle pulse wave velocity Dropouts: 10 intervention, 11 control Available outcomes: BMI, lipids, BP, HbA1c, cancer diagnosis (BP data not used as groups very different at baseline) Response to contact: not yet attempted	
Notes	Trial funding: not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly divided into 2 groups matched for age and gender
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors of main trial outcomes were blinded to the treatment

Mita 2007 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rate (26%) over 2 years. All dropouts explained, however, 5 were excluded for poor compliance but no clear predefined protocol for exclusion
Selective reporting (reporting bias)	Unclear risk	No protocol
Attention bias	Low risk	All participants had the same contact
Compliance	Low risk	No tissue fatty acids reported, but TC lower in intervention arm (5.37 mmol/L SD 0.74 at baseline, 5.15 mmol/L SD 0.83 at 2 years), than control (5.37 mmol/L SD 1.03 at baseline, 5.27 mmol/L SD 0.99 at 2 years)
Other bias	Low risk	None noted

MRC 1968

Methods	Medical Research Council (MRC) RCT, 2 arm, parallel (n6 LA vs mixed fats), 4 years Summary risk of bias: moderate to high
Participants	Free-living men who have survived a first MI (UK) CVD risk: high Control: randomised 194, analysed 181 at 2 years Intervention: randomised 199, analysed 172 at 2 years Mean years in trial: control 3.7, intervention 3.8 % male: 100 Age: unclear Age range: all < 60 years Smokers: control 84%, intervention 81% Hypertension: control 12%, intervention 8% Medications taken by $\geq 50\%$ of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK Ethnicty: not reported
Interventions	Type: diet advice plus supplement Comparison: soya oil (n-6) vs usual diet (some SFA replacement, otherwise unclear) Control aims: usual diet Intervention aims: reduce dietary fat to 35 g/d fat, add 84 g/d soya oil Dose aim: increase 84 g/d soya oil or 756 kcal or 37.8% E soya (assume 50% LA, so 18.9% E LA, assume 58% PUFA so21.9% E PUFA) Baseline PUFA: unclear Compliance by biomarkers: serum TC reported but without variance info, but TC

	ower in intervention than control consistently post-baseline. Report stated that, "tissue fat of the men on the soya-bean oil diet was less saturated than that of the controls" and that further information would be published elsewhere. No statistical significance or variance data mentioned Compliance by dietary intake: unclear • Energy intake, kcal/d: intervention 2380 (SD not reported), control 2274 (SD not reported) • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • MUFA intake: not reported • CHO intake, g/d: intervention 243 (SD not reported), control 228 (SD not reported) • Sugars intake, g/d: intervention 66 (SD not reported), control 60 (SD not reported) • Protein intake, g/d: intervention 80 (SD not reportedR), control 88 (SD not reported) • Alcohol intake: not reported Compliance, other methods: not reported Inclusion basis: aimed to replace SFA with PUFA. PUFA dose: 21.9% E PUFA (aim) Duration of intervention: 4 years	
Outcomes	Main trial outcomes: MI or sudden death Dropouts: intervention 199 randomised, 181 at 2 years, 91 at 4 years. Control: 194 randomised, 172 at 2 years, 85 at 4 years Available outcomes: mortality, CV mortality (CV deaths plus non-fatal MI), total MI, non-fatal MI (data for weight, TC and BP, but no variance info) Response to contact: reply from trial statistician, JA Heady, in 1999	
Notes	Some data not usable due to lack of variance. For all, data at 4 years, control N = 89, intervention N = 88 Weight change: intervention 0 kg, control -3 kg TC change: intervention -1.11 mmol/L, control -0.47 mmol/L Systolic BP change: intervention +2 mmHg, control 0 mmHg Diastolic BP change: intervention -1 mmHg, control +3 mmHg Trial funding: Medical Research Council	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using random numbers, by blocks within hospitals"
Allocation concealment (selection bias)	Unclear risk	Not described

MRC 1968 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Big changes to fat intake in intervention group while control group ate their usual diet
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Suspected relapses were assessed at regular intervals by a review committee unaware of the patients diet group"
Incomplete outcome data (attrition bias) All outcomes	High risk	Data collection was thorough, but some participants dropped out and contact was lost
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	High risk	Dietary intervention, control ate usual diet, so likely that intervention group received more time and support, though this is not clear from paper
Compliance	Low risk	TC lower in intervention than control consistently post-baseline. Report stated that "tissue fat of the men on the soya-bean oil diet was less saturated than that of the controls" and that further information would be published elsewhere
Other bias	Low risk	None noted

NDHS Faribault 1968

Methods	National Diet-Heart Study (NDHS) - Faribault site RCT, several arms, parallel (n6 LA vs SFA), 1 year Summary risk of bias: low
Participants	Men living in a mental health institute CVD risk: low N: interventions B, C, E combined: randomised 167, analysed 143; control: randomised 57, analysed 52 Mean years in trial: interventions 0.9, control 1.0, % male: 100 Age: unclear Age range: all 45-54 years Smokers: 55%-59% current smokers in each arm Hypertension: unclear Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA

	Ethnicty: not reported
Interventions	Type: diet provided (residential institution) Comparison: PUFA (n-6) vs usual institutional diet (SFA and MUFA) Control aims: total fat 40% E, SFA 16%-18% E, dietary cholesterol 650-750 mg/d, P/S 0.4 (so PUFA 6.8% E) (whole diet provided) Intervention aims: B (C, E) total fat 30% E (40% E, 40% E), SFA < 9% E (< 9% E, not stated), dietary cholesterol 350-450 mg/d (350-450 mg/d, not stated), PUFA 15% E (18-20% E, not stated), P/S 1.5 (2.0, 4.4) (equivalent to Minnesota Coronary Trial diet) (whole diet provided) Dose aim: increase B 8.2% E, C 12.2% E, E unclear n-6 Baseline n-6 (table IX2): 4.4% E LA, 4.8% E PUFA Compliance by biomarkers: serum TC significantly reduced in intervention compared to control (-0.91 mmol/L, 95% Cl -1.17 to -0.65). Fatty acid composition of red blood cells suggests that LA was higher in intervention arms (table X6: LA rose by 4 in control, by 5-7 in other arms, at the expense of MUFA, which rose by 1 in control, felb y4 or 5 in other arms. Palmitic acid fell by 5 in control, and fell by 4 in intervention arms, stearic did not alter in control, rose by 1 or 2 in intervention arms - no statistical significance or variance info provided, units unclear, probably % of LA+oleic+palmitic+stearic) Compliance by dietary intake good. Assessed from 7-day food records after 28 and 44 weeks combined (tables IX8&9) • Energy intake, kcal/d: intervention B 2549, intervention C 2599, intervention E 2560, control D 2593 • Total fat intake, % E: intervention B 29.0, intervention C 38.5, intervention E 37.1, control 39.5 (decrease B 10.5% E, C 1.0% E, E 2.4 total fat) • SPA intake, % E: intervention B 6.1, intervention C 7.0, intervention E 4.6, control D 15.6 (decrease B 9.5% E, C 8.6% E, E 11.0% E SFA) • PUFA n-3 intake: not reported • PUFA n-6 intake, % E: intervention B 11.6, intervention C 17.8, intervention E 22.3, control D 4.6 (increase B 7.5% E, C 13.2% E, E 17.7% E PUFA) • CHO intake, % E: intervention B 55.3, intervention C 13.7, intervention E 18.6, control D 19.3 (decrease B 8.5% E, C
Outcomes	Main trial outcomes: lipid levels and dietary assessment Dropouts: B 7, C 10, E 7, D (control) 5

NDHS Faribault 1968 (Continued)

	Available outcomes: mortality, TC (weight and TG data available but without SDs) Response to contact: not attempted as trial completed in 1967
Notes	Data entered as all interventions combined (B+C+E) vs control (D) Dose calculations Interventions: B PUFA 15% E, 8.2% E Control: 17% E SFA, P/S 0.4 so PUFA 6.8% E C PUFA 19% E, 12.2% E D unclear % E? Mean for all interventions 10.2% E Trial funding: National Heart Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Institution so all participants and trial staff blinded to allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were reported as blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Institution so able to follow-up all participants through trial
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention bias	Low risk	Equivalent, diet provided to both groups
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.91 mmol/L, 95% CI -1.17 to -0.65). Fatty acid composition of red blood cells suggests LA was higher in intervention arms
Other bias	Low risk	None found

NDHS Open 1st 1968

Methods	National Diet-Heart Study (NDHS) - open first phase RCT, several arms, parallel (n6 LA vs SFA), 1 year Summary risk of bias: low
Participants	Free-living men aged 45-54 years CVD risk: low
	Interventions B, C, X combined: randomised 829, analysed 726 Control: randomised 382, analysed 341
	Mean years in trial: control 0.95, Interventions 0.93
	% male: 100
	Age: unclear
	Age range: all 45-54 years
	Smokers: 39%-40% current smokers in each arm
	Hypertension: unclear
	Medications taken by \geq 50% of those in the control group: not reported
	Medications taken by 20%-49% of those in the control group: not reported
	Medications taken by some, but < 20% of the control group: not reported Location: USA
	Ethnicty: white 98.2%, non-white 1.8% (not reported by intervention arm)
Interventions	Type: diet provided (bought from a trial shop)
	Comparison: PUFA (n-6) vs usual diet (replacement of SFA and MUFA)
	Control aims: total fat 40% E, dietary cholesterol 650-750 mg/d, P/S 0.4 (assume PUFA
	6.8% E as at Faribault) (foods bought from a trial shop - normal foods)
	Intervention aims: B (C, X) total fat 30% E (40% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E), SFA < 9% E (< 9% E, 30% E)
	9% E), dietary cholesterol 350-450 mg/d (350-450 mg/d, 350-450 mg/d), PUFA 15% E (18% E-20% E, 15% E), P/S 1.5 (2.0, 1.5) (foods bought from a trial shop - SFA
	removed and replaced by polyunsaturated oils and fats)
	Dose aim: increase B 8.2% E, C 12.2% E, X 8.2% E n-6
	Baseline n-6 (tables IX 1&3): 3.7% LA, 3.9% PUFA
	Compliance by biomarkers: serum TC significantly reduced in intervention compared
	to control (-0.45 mmol/L, 95% CI -0.55 to -0.35). Data on fatty acid composition o red blood cells provided in chapter 10 (table X6: LA rose by 1 in control, by 2-3 in other arms, at the expense of MUFA which did not alter in control, fell by 2-3 in othe
	arms. Palmitic acid remained constant in control and remained constant or fell by 1 in
	intervention arms, stearic did not alter in control and remained constant or rose by
	in intervention arms - no statistical significance or variance info provided, units unclear
	probably % of LA+oleic+palmitic+stearic)
	Compliance by dietary intake: good. Nutritionists' subjective adherence ratings o
	excellent or good (as compared to fair or poor) intervention B 58%, intervention C 60% control D 55%. Dietary intake computed from 7-day food records at 28 weeks (table
	IX3, no later data found):
	• Energy intake, kcal/d: intervention B 2154 (SD432), intervention C 2262
	(SD435), intervention X 2117 (SD447), control D 2228 (SD456) • Total fat intake, % E: intervention B 29.7, intervention C 34.4, intervention X
	31.7, control D 34.9 (decrease B 5.2% E, C 0.5% E, X 3.2 total fat)
	• SFA intake, % E: intervention B 7.1, intervention C 7.4, intervention X 8.9,
	control D 11.6 (decrease B 4.5% E, C 4.2% E, X 2.7% E SFA)
	• PUFA intake, % E: intervention B 9.9, intervention C 13.2, intervention X 6.5,

	 control D 4.9 (increase B 5.0% E, C 8.3% E, X 1.6 PUFA) PUFA n-3 intake: not reported PUFA n-6 intake: not reported, probably similar to PUFA Trans fat intake: not reported MUFA intake, % E (by subtraction of SFA and PUFA from total fat): intervention B 12.7, intervention C 13.8, intervention X 16.3, control D 18.4 (decrease B 5.7% E, C 4.6% E, X 2.1% E MUFA) CHO intake, % E: intervention B 48.7, intervention C 45.3, intervention X 49. 5, control D 44.7 (increase B 4.0% E, C 0.6% E, X 4.8% E CHO) Sugars intake: not reported Protein intake, % E: intervention B 18.6, intervention C 17.6, intervention X 17. 1, control D 17.4 (increase B 1.2% E, C 0.2% E, X -0.3% E protein, little change) Alcohol intake, % E: intervention B 2.1, intervention C 2.1, intervention X 1.7, control D 2.2 (minimal change) Compliance, other methods: also assessed adherence ratings by nutritionists, subjectively, by recall and by food records. Poor adherence by 17%-29%, others were fair, good or excellent Inclusion basis: aimed to increase PUFA intake as well as increase PUFA/SFA, reduce SFA slightly and reduce dietary cholesterol PUFA dose: achieved B 5.0% E, C 8.3% E, X 1.6 PUFA Duration of intervention: 1 year
Outcomes	Main trial outcomes: lipid levels and dietary assessment Dropouts: intervention B 42, C 34, X 5, control D 36 Available outcomes: CV events (MI and PAD events), cancer diagnoses, TC (weight, diastolic BP and TG data available but without SDs) Response to contact: not attempted as trial completed in 1967
Notes	All intervention arms combined for data analysis Aim was to replace saturates with polyunsaturates, but oils used were omega-6 fats Dose calculations Control: assume from Faribault 17% E SFA, P/S 0.4 so PUFA 6.8% E Interventions: B PUFA 15% E, 8.2% E C PUFA 19% E, 12.2% E X PUFA 15% E, 8.2% E Mean for all interventions 10% E Trial funding: National Heart Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	Stratified randomisation by the statistical centre

NDHS Open 1st 1968 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and trial personnel (aside from the store manager) were blinded to alloca- tion. Blinding of participants was checked using a questionnaire, which found no dif- ference between intervention and control participants in guesses at dietary composi- tion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were reported as blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% dropouts, well described
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry entry found
Attention bias	Low risk	Equivalent, both groups bought special foods from trial shop
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.45 mmol/L, 95% CI -0.55 to -0.35). Data on fatty acid composition of red blood cells shows LA rose by 1 in control, by 2-3 in other arms, at the expense of MUFA, which did not alter in control, fell by 2 or 3 in other arms
Other bias	Low risk	None noted

Nodari 2011 AF

Methods	RCT, parallel, (n3 DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	Adults with persistent AF with ≥ 1 relapse after cardioversion N: 102 intervention, 103 control (analysed, intervention: 94 control: 94) Level of risk for CVD: high Male: 70% intervention, 63% control Mean age (SD): 70 (6) intervention, 69 (9) control Age range: not reported (18-80 inclusion criteria) Smokers: 10% intervention, 9.1% control Hypertension: 47% intervention, 40% control Medications taken by $\geq 50\%$ of those in the control group: beta-blockers, ACE inhibitors, anticoagulant therapy, amiodarone Medications taken by 20%-49% of those in the control group: diuretics, antiplatelet, statins Medications taken by some, but < 20% of the control group: Ca channel blockers

Nodari 2011 AF (Continued)

	Location: Italy Ethnicity: not reported	
Interventions	Type: supplement (Omacor) Comparison: EPA and DH+A vs MUFA Intervention: 2 x1 g/d Omacor (total 1.7 g/d EPA + DHA at a ratio of 0.9-1.5) Control: 2 x1 g/d olive oil (gelatin capsules identical in appearance to Omacor) Dose aim: increase 1.7 g/d EPA + DHA, 0.8% E n-3, 0.8% E PUFA Baseline PUFA not reported Compliance by biomarkers: unclear, no biomarkers, no TC reported. Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • Inclusion basis: intended dose was an increase 1.7 g/d EPA + DHA without differences in other PUFAs, so assumed dose 0.8% E PUFA, > 10% increase in total PUFA from assumed baseline of 6% E. No biomarker, TC or dietary intake data to support this PUFA dose: 0.8% E	
Outcomes	Duration of intervention: 12 months Main trial outcome: probability of maintenance of sinus rhythm	
Catconics	Dropouts: 6 intervention, 5 control Available outcomes: adverse events, AF recurrence (nil death) Response to contact: no (contact established with trial author but no data received in this trial)	
Notes	Trial funding: 'Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco' of the University of Brescia, Brescia, Italy. The work of Dr Campia was supported by National Institutes of Health grant K12 HL083790-01a1	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment followed a computer- generated randomisation list obtained us- ing blocks of size 4

Nodari 2011 AF (Continued)

Allocation concealment (selection bias)	Low risk	The randomisation schedule was kept in the research pharmacy area and was available only to unblinded pharmacy personnel until after the database was locked. At that time, the unblinded patient treatment information was made available to the investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo gelatin capsules identical in appearance to Omacor. However no information provided as to their smell and taste
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised were accounted for. ITT for main outcomes
Selective reporting (reporting bias)	Unclear risk	NCT01198275. Registered retrospectively in September 2010, trial started January 2006, completed May 2008, main publication 2011
Attention bias	Low risk	No difference between groups
Compliance	Unclear risk	No biomarkers, no TC reported
Other bias	Low risk	None noted

Nodari 2011 HF

Methods	RCT, parallel, (n3 DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with heart failure (non-ischaemic dilated cardiomyopathy) N: 67 intervention, 66 control (analysed, intervention: 67 control: 66) Level of risk for CVD: high Male: 95.5% intervention, 84.9% control Mean age (SD): 61 (11) intervention, 64 (9) control Age range: not reported (18-75 inclusion criteria) Smokers: not reported Hypertension: not reported Medications taken by $\geq 50\%$ of those in the control group: beta-blockers, ACEi, furosemide, amiodarone, aldosterone blockers Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: statins, ARB Location: Italy

Nodari 2011 HF (Continued)

	Ethnicity: not reported	
Interventions	Type: supplement (Omacor) Comparison: EPA + DHA vs MUFA Intervention: 2 x1 g/d Omacor (1.7 g/d EPA + DHA at a ratio of 0.9:1.5) Control: 2 x1 g/d olive oil (gelatin capsules identical in appearance to Omacor) Dose aim: increase 1.7 g/d EPA + DHA, 0.8% E n-3, 0.8% E PUFA Baseline PUFA not reported Compliance by biomarkers: circulating free fatty acid EPA + DHA 0.83% of circulating FFAs in intervention group, 0.41% in control group, but no omega-6 or total PUFA reported. TC equivalent at baseline (187 mg/dL) and similar at 1 year (4.8 mmol/L, SD 0.62 intervention, 4.9 mmol/L, SD 0.62 control) Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Energy intake, kcal/d: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • PUFA intake, % E: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • Alcohol intake, % E: not reported • Protein intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported • Protein intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported • Protein intake, % E: not reported	
Outcomes	Main trial outcome: left ventricular function and functional capacity Dropouts: 0 intervention, 0 control Available outcomes: mortality (nil death), combined CVD events, AF, BMI, hospitalisation for CV reasons, hospitalisation for worsening heart failure, lipids, blood glucose (but too different at baseline to use), serum cytokine Response to contact: yes, additional data and methodological data provided	
Notes	Trial funding: Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco, one author was a consultant for 8 pharmaceutical companies	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"

Nodari 2011 HF (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Paper states that placebo and verum were identical and that the trial was double-blind, but blinding of participants not checked. Trial author confirmed investigators not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial author confirmed assessors not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all participants were assessed for all outcomes (e.g. hospitalisation) , but some outcomes report no attrition
Selective reporting (reporting bias)	Unclear risk	NCT01223703 - trial registration Octpber 2010, recruitment November 2007-June 2009. Retrospective
Attention bias	Low risk	No suggestion of this, and investigators appeared blinded (so could not differ in attention provided by allocation)
Compliance	High risk	Circulating free fatty acid EPA + DHA 0.83% of circulating FFAs in intervention group, 0.41% in control group, but no omega-6 or total PUFA reported. TC equivalent at baseline (187 mg/dL) and similar at 1 year (4.8 mmol/L, SD 0.62 intervention, 4.9 mmol/L, SD 0.62 control)
Other bias	Low risk	None noted

Nye 1990

Methods	Randomisation: parallel, 3 groups (n3 EPA vs MUFA vs aspirin and dipyridamole), 1 year Risk of bias: moderate or high
Participants	People undergoing percutaneous transluminal coronary angioplasty N: 36 intervention, 37 control (also 35 allocated to arm 3, aspirin and dipyridamole) Level of risk for CVD: high (people undergoing angioplasty) Male: 78% intervention, 76% control Mean age (SD): 54 (8) intervention, 55 (8) control years Age range: unclear Smokers: unclear Hypertension: unclear

Nye 1990 (Continued)

	Medications taken by $\geq 50\%$ of those in the Medications taken by 20%-49% of those in Medications taken by some, but < 20% of Location: New Zealand Ethnicity: unclear	n the control group: not reported
Interventions	Type: supplement (capsules) Comparison: EPA vs MUFA Intervention: maxEPA capsules 12/d (2.2 g EPA) Control: olive oil capsules, 12/d, identical to MaxEPA. Both capsules had vit E Dose aim: increase 2.2 g/d EPA + DHA, 1.0% E n-3, 1.0% E PUFA Baseline PUFA not reported Compliance by biomarkers: plasma EPA increased in the intervention group by 0.49 mmol/L (95% CI 0.34-0.64), while were "unchanged" in the control group, but no other PUFA data were presented. However, TC appeared higher in the intervention group (6. 55 mmol/L, SD 1.09 in intervention, 6.07 mmol/L, SD 1.33 in control, presumably at the end of the intervention) Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • PUFA intake, % E: not reported • PUFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • Trans fat intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • CHO intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported Inclusion basis: intended dose was an increase 2.2 g/d EPA + DHA. With no suggestion of differences in other PUFAs assumed dose was 1.0% E PUFA, > 10% increase in total PUFA from assumed baseline of 6%E. No biomarker or dietary intake data but challenged by TC PUFA dose: 1.0% E	
Outcomes	Main trial outcome: angina, restenosis Dropouts: none Available outcomes: angina, interventions, lipids (nil death) Response to contact: not attempted	
Notes	Trial funding: Medical Rsearch Council of New Zealand and Scherer Ltd (who supplied MaxEPA and the olive oil capsules)	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Nye 1990 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided without exclusions into 3 groups"
Allocation concealment (selection bias)	Unclear risk	Unclear, no further info
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States that placebo capsules were identical to the MaxEPA, and Quote: "neither the patient nor the attending cardiologist knew which capsules were being used" But no masking of taste was reported, and participant guesses as to allocation were not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the patient, nor the attending cardiologist knew which capsules were being used" "Angioplasty was repeated electively at one year or before where symptoms recurred, and assessed without knowledge of the patient's treatment group."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some participants were lost to follow-up and reasons for this were unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Attention bias	Low risk	No suggestion of attention bias, symptomatic participants were reviewed between scheduled visits, otherwise all on the same schedule
Compliance	High risk	Plasma EPA increased in the intervention group by 0.49 mmol/L (95% CI 0.34-0. 64), while were "unchanged" in the control group, but no other PUFA data were presented. However, TC appeared higher in the intervention group (6.07 mmol/L, SD 1.33 in control, 6.55 mmol/L, SD 1.09 in intervention, presumably at the end of the intervention)
Other bias	Low risk	No further bias noted

ORL 2013

Methods	RCT- parallel, 3 arms (n3 EPA + DHA high dose vs n3 EPA + DHA low dose vs n3 EPA), 12 months Summary risk of bias: moderate or high
Participants	Population: Japanese adults with hypertriglyceridaemia N: 171 intervention (4 g TAK), 165 control (2 g TAK) Level of risk for CVD: moderate Male: 70.8% intervention, 71.5% control Mean age (SD): 55.9 (10.12) intervention, 56 (10.95) control Age range: 20-74 Smokers (current): 27.5% intervention, 31.5% control Hypertension: 66.7% intervention, 67.3% control Medications taken by \geq 50% of those in the control group: not reported Medications taken by some, but < 20%: not reported Location: Japan Ethnicity: unclear
Interventions	Type: supplement (TAK-085 capsules) Comparison: EPA + DHA higher vs lower dose Intervention: 1 x2 /d capsule each containing 2 g of TAK-085 (1 g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 1.86 g/d EPA & 1.5 g/d DHA Control: 1 capsule/d containing 2 g of TAK-085 (1 g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E) Total dose of 0.93 g/d EPA and 0.75 g/d DHA Dose aim high TAK vs low TAK: increase 1.68 g/d EPA + DHA, 0.8% E n3, 0.8% E PUFA assumed (no details of other capsule components provided) Baseline PUFA not reported Compliance by biomarkers: plasma free fatty acids did not differ between high and low TAK for AA, while EPA and DHA were higher in high TAK by 52 weeks. There was a small difference in change in TC between high and low TAK, statistical significance unclear Compliance by dietary intake: not reported Energy intake, kcal/d: not reported Energy intake, kcal/d: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported PUFA n-6 intake: not reported PUFA intake, % E: not reported PUFA intake, % E: not reported AUFA intake, % E: not reported Alcohol intake: not reported

ORL 2013 (Continued)

	TAK, and no suggestion of different intakes of other PUFAs between arms PUFA dose: 0.8% E Duration of intervention: 12 months
Outcomes	Main trial outcome: safety outcomes and adverse events Dropouts: 8 G1, 14 G2, 21 G3 Available outcomes: adverse events (including CVD events, cancers), CRP, waist circumference, weight, BP (nil death), lipids provided as % change from baseline, but no baseline data available, so not used in meta-analyses Response to contact: contact attempted but no response to date
Notes	A third arm of EPA-E 1.8 g supplementation is not used here. Outcome data used TAK-4 vs TAK-2 Trial funding: funded by Takeda Pharmaceutical Company

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to statin use and performed by an independent registration centre
Allocation concealment (selection bias)	Low risk	Randomisation was stratified according to statin use and performed by an independent registration centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open- label
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and analysed for main outcomes
Selective reporting (reporting bias)	Low risk	Trials registry entry May 2011, trial start date November 2009, completion November 2011, so partially retrospective. However, entry appears to reflect reported outcomes
Attention bias	Low risk	Capsules, appeared equivalent
Compliance	Unclear risk	Plasma free fatty acids did not differ be- tween high and low TAK for AA, while EPA and DHA were higher in high TAK

ORL 2013 (Continued)

		by 52 weeks. There was a 1% difference in change in TC between high and low TAK, statistical significance unclear	
Other bias	Low risk	None noted	
PREDIMED 2013			
Methods	RCT, parallel, 3 arms (high oil), also low-fat arm, 60 m	PREvención con Dieta MEDiterránea (PREDIMED) RCT, parallel, 3 arms (high PUFA vs low PUFA, Mediterranean diet with nuts or olive oil), also low-fat arm, 60 months Summary risk of bias: moderate to high	
Participants	≥ 3 CVD risk factors N: intervention (Med with arm, not discussed here, 24 Level of risk for CVD: moc Male: intervention 46%, cc Mean age (SD): interventio Age range: 55-80 years Smokers: intervention 14.5 Hypertension: intervention Medications taken by ≥ 50 Medications taken by 20% antihypertensives, statins, o Medications taken by some lowering, hormone replacer Location: Spain	N: intervention (Med with nuts) 2454, control (Med with olive oil) 2543 - also low-fat arm, not discussed here, 2450 Level of risk for CVD: moderate Male: intervention 46%, control 41.3% Mean age (SD): intervention 67 (6), control 67 (6) years Age range: 55-80 years Smokers: intervention 14.5%, control 13.9% (current smokers) Hypertension: intervention 82.4%, control 82.1% Medications taken by ≥ 50% of those in the control group: nil Medications taken by 20%-49% of those in the control group: ACEi, diuretics, other antihypertensives, statins, oral hypoglycaemics, antiplatelet therapy Medications taken by some, but < 20% of the control group: insulin, non-statin lipid-lowering, hormone replacement therapy Location: Spain Ethinicty: white from Europe 97%, Hispanic from Central or South America 1%-2%,	
Interventions	Comparison: PUFA vs MU Intervention: Mediterranea hazelnuts, 7.5 g almonds, p diet with individual and up Control: Mediterranean die intensive education on diet Dose aim : unclear, food ra (MUFA) Baseline PUFA 6.4% E in i Compliance by biomarket Compliance by dietary in quency questionnaire • Energy intake, kcal/d: • Total fat intake, % E: (SD 5.4)	Baseline PUFA 6.4% E in intervention, 6.1% E in control Compliance by biomarkers: unclear, no serum TC reported, no tissue fatty acids Compliance by dietary intake: all assessed at end of trial using a 137-item food frequency questionnaire • Energy intake, kcal/d: intervention 2229 (SD 477), control 2172 (SD 475) • Total fat intake, % E: intervention 41.5 (SD 6.1) (MD +0.4% E), control 41.2	

	 PUFA intake, % E: intervention 7.7 (SD 1.8), (MD +1.6% E), control 6.1 (SD 1.4) PUFA n-3 intake (ALA plus marine omega-3), g/d: intervention 2.7 (SD not reported), (MD +0.5 g/d), control 2.2 (SD not reported) PUFA n-6 intake, g/d: LA, intervention 16.0 (SD 5.5), (MD +3.8 g/d), control 12.2 (SD 4.6) g Trans fat intake: not reported MUFA intake, % E: intervention 20.9 (SD 4.1), (MD -1.2% E), control 22.1 (SD 3.7) CHO intake, % E: intervention 39.7 (SD 6.3), (MD -0.7% E), control 40.4 (SD 5.9) Sugars intake: not reported Protein intake, % E: intervention 16.4 (SD 2.5), (MD 0.2% E), control 16.2 (SD 2.4) Alcohol intake, % E: not reported Compliance by other methods: scores on the 14-item Mediterranean-diet screener increased for the participants in both Mediterranean diet groups. Participants assigned to a Mediterranean diet with nuts significantly increased their consumption of extra virgin olive oil (to 50 g/d and 32 g/d, respectively) and nuts (to 0.9 and 6 servings/week, respectively) Inclusion basis: dietary intake data suggested total PUFA intake 1.6% E higher in intervention than control PUFA dose: 1.6% E Duration of intervention: 56 months median
Outcomes	Main trial outcome: CVD events Dropouts: intervention 6.3% lost to follow-up for ≥ 2 years, control 3.6% lost to follow-up for ≥ 2 years Available outcomes: deaths, CV mortality, stroke, MI, CV events. Outcome data not altered in the republication of the main paper (Estruch 2018) Response to contact: contact established but no additional data provided
Notes	All data used were for the Mediterranean diet with nuts vs Mediterranean diet with olive oil, which is higher vs lower PUFA. As nuts were mixed it is not clear whether they were high in ALA or not (probably varied) Trial funding: mainly governmental funding, but olive oil and nuts were provided by companies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Tables of random allocation were centrally elaborated. However the main paper (Estruch 2013) was retracted and republished (as Estruch 2018) following a statistical analysis suggesting that baseline variables did not appear consistent with randomisation (Carlisle 2017). The republication

PREDIMED 2013 (Continued)

		states that partners were included in the trial without randomisation (in the same arms as family members) and that some clinics allocated by clinic rather than applying the protocol specified individual randomisation. This puts allocation concealment of some participants at high risk
Allocation concealment (selection bias)	High risk	Trial nurses in charge of the random allocation were independent of the nursing staff, allocation was performed centrally. However, see note on random sequence generation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Olive oil and nuts arms could not be blinded to participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All medical records related to end points were examined by the end-point adjudication committee, whose members were unaware of the trial-group assign- ments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We used four sources of information to identify end points: repeated contacts with participants, contacts with family physicians, a yearly review of medical records, and consultation of the National Death Index." Attrition was < 10% per year, explained and balanced.
Selective reporting (reporting bias)	High risk	Many outcomes in the trials registry entry are not reported by allocated group for the full set of trial participants (for example, cognition)
Attention bias	Low risk	These appear very similar between the two Mediterranean diet groups
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	High risk	Retraction and republication in 2018 due to randomisation problems not reported in the initial publication. However, new outcome data not provided

Proudman 2015

Methods	RCT, parallel, (n3 EPA + DHA high dose vs n3 EPA + DHA low dose), 12 months Summary risk of bias: low
Participants	People with rheumatoid arthritis < 12 months' duration, disease-modifying anti- rheumatic drugs (DMARD)-naive N: 87 intervention, 53 control (analysed, intervention: 75 control: 47) Level of risk for CVD: low Male: 29% intervention, 25% control Mean age (SD): 56.1 (15.9) intervention, 55.5 (14.1) control Age range: unclear Smokers: 65.1% intervention, 54.7% control (includes current & previous smokers) Hypertension: not reported Medications taken by ≥ 50% of those in the control group: triple DMARD therapy (sulfasalazine 0.5 g/d, hydroxychloroquine 200 mg twice/day and methotrexate 10 mg once/week) Medications taken by 20%-49% of those in the control group: NSAIDS Medications taken by some, but < 20% of the control group: oral or parenteral steroids Location: Australia Ethnicity: not reported
Interventions	Type: supplement (fish oil) Comparison: high EPA + DHA vs low EPA + DHA + MUFA Intervention: 10 mL/d fish oil concentrate (BLT Incromega TG3525) providing 5.5 g/d (3.2 EPA + 2.3 DHA) Control: 10 mL/d Sunola oil:capelin oil (2:1) providing 0·21 g EPA + 0·19 g/d DHA as TG (0.40 g/d EPA + DHA). Sunola oil was stated to be a monounsaturated oil Dose aim: increase 5.1 g/d EPA + DHA, 2.3% E n-3, 2.3% E PUFA Baseline PUFA not reported Compliance by biomarkers: unclear, no serum TC reported, plasma phospholipid EPA and DHA reported, but not by intervention group, no other tissue fatty acids reported Compliance by dietary intake: not reported Energy intake, kcal/d: not reported Energy intake, kcal/d: not reported SFA intake, % E: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported PUFA n-6 intake: not reported MUFA intake, % E: not reported CHO intake, % E: not reported Alcohol intake, % E: not reported Compliance by other methods: consumption checked at each visit. 100% compliance would be consumption of 3650 mL oil at 12 months. The fish oil group was less compliant than the control group with median intakes of 2482 mL and 3248 mL, respectively (P = 0.015, Mann-Whitney U test). This provided an average daily intake of EPA + DHA of 3.7 g and 0.36 g in the fish oil and control groups, respectively Inclusion basis: compliance data suggested that omega-3 fats increased by 3.3 g/d EPA

Proudman 2015 (Continued)

	+ DHA, or 29.7 kcal/d, or 1.5% E. This is > 10% increase of assumed 6% E total PUFA intake at baseline, assuming no or minor PUFA in control (described as MUFA oil) PUFA dose: 1.5% E total PUFA Duration of intervention: 12 months
Outcomes	Main trial outcome: DMARD failure and remission Dropouts: 11 intervention, 6 control Available outcomes: mortality (nil death), adverse events including CVD, Disease Activity Score, diabetes, BMI change Response to contact: yes, trial authors supplied methodology data plus BMI change
Notes	DAS scores are reported as median and IQR in Proudman 2012 abstract (see Proudman 2015) Trial funding: the trial was supported by 'the National Health Medical Research Council of Australia and Royal Adelaide Hospital Research Committee. Melrose Health has provided support for ongoing studies.' The oil used in the trial was made by the Royal Adelaide Hospital Pharmacy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was prepared using an online random num- ber generator and involved randomly per- muted blocks of size six."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed by the RAH pharmacy, which also prepared and provided the study oils in 500 mL iden- tical dark brown bottles labelled with con- secutive study numbers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both participants and investiga- tors/assessors were blinded to the group al- location. Although the control oil was paler in colour than the fish oil, this was not evi- dent in the brown bottles. The 'fishy' odour of each oil was similar."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both participants and investiga- tors/assessors were blinded to the group al- location" Quote: "Investigators and subjects re- mained blinded for all withdrawals."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The flow of all trial participants shown in FIGURE 2

Proudman 2015 (Continued)

Selective reporting (reporting bias)	Unclear risk	Outcomes reported in trial register matched with the outcomes reported in publications. However, the trial was retrospectively registered - registered in 2013, recruitment began in 2001
Attention bias	Low risk	No difference between groups
Compliance	Unclear risk	No TC reported, plasma phospholipid EPA and DHA reported, but not by intervention group, no other tissue fatty acids reported
Other bias	Low risk	None noted

Puri 2005

Methods	RCT, parallel (n3 EPA vs non-fat), 2 arms, 12 months Summary risk of bias: low
Participants	People with Huntington's disease N: 67 intervention, 68 control (analysed, intervention: 39 control: 44) Level of risk for CVD: low Male: 57% intervention, 44% control Mean age (SD): 50 (9.3) intervention, 49 (9.0) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: antidepressants Medications taken by some, but < 20%: neuroleptics Location: Australia, Canada, UK, USA Ethnicity: white (black, Asian) 94% (4%, 1%) intervention, 97% (3%, 0%) control
Interventions	Type: supplement (ethyl-EPA) Comparison: EPA vs paraffin (non-fat) Intervention: 2 x 2 x 500 mg capsules/d, total dose of 2 g/d ethyl-EPA (code name LAX-101, purity 95%) Control: 2 x 2 x 500 mg capsules/d liquid paraffin Dose aim: increase 1.9 g/d EPA + DHA, 0.86% E n-3, 0.86% E PUFA Baseline PUFA not reported Compliance by biomarkers: no serum TC reported, no tissue fatty acids reported Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported

Puri 2005 (Continued)

	 PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake, % E: not reported CHO intake, % E: not reported Sugars intake: not reported Protein intake, % E: not reported Alcohol intake, % E: not reported Alcohol intake, % E: not reported Compliance by other methods: 38 were excluded for protocol violations, 4 intervention and 16 control were non-compliant with capsules Inclusion basis: intended that omega-3 fats increased by 1.9 g/d EPA + DHA, or 0.86% E from omega-3 fats. This was compared to paraffin (no fat), so dose of total PUFA was 0.86% E. This is > 10% increase of assumed 6% E total PUFA intake at baseline PUFA dose: 0.86% E total PUFA Duration of intervention: 12 months
Outcomes	Main trial outcome: functional status in Huntington's disease Dropouts: 7 intervention, 7 control Available outcomes: measures of functional capacity, CV events, cancers (no deaths) Response to contact: yes (replied to say that no CV mortality or fatal MI occurred)
Notes	Trial funding: "Amarin Neuroscience Ltd. (formerly known as Laxdale Ltd.) was responsible for organizing and funding this clinical trial" as well as paying the salaries of several investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After screening and acceptance patients were assigned to treatment by receiving a numbered pack supplied by a clinical trials packaging organization independent of all other aspects of the trial. Randomization was stratified in a block size of four, with the appropriate number of blocks allocated to each centre. PCI Clinical Services held the randomization code until the database had been closed and all patients had been assigned"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo and ethyl-EPA capsules were of identical appearance" (though taste and smell not reported)

Puri 2005 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation described as "double-blind", "neither the participants nor the participating medical staff had access to this code during the course of the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Clearly reported and complete, however > 20% attrition
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry identified
Attention bias	Low risk	Unlikely
Compliance	Unclear risk	No TC or tissue fatty acids reported
Other bias	Low risk	None noted

Raitt 2005

Methods	RCT, parallel, (n3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	People with implantable cardioverter defibrillators and recent sustained VT/VF N: 100 intervention, 100 control Level of risk for CVD: high Male: 86% intervention, 86% control Mean age (SD): 63 (13) intervention, 62 (13) control Age range: not reported but 18-75 inclusion criteria Smokers: not reported Hypertension: 46% intervention, 55% control Medications taken by \geq 50% of those in the control group: diuretic, beta blockers, ACEi Medications taken by 20%-49% of those in the control group: digoxin, statins Medications taken by some, but < 20% of the control group: Ca channel blocker Location: USA Ethnicity: white 94% intervention, 97% control
Interventions	Type: supplement (fish oil capsules vs olive oil capsules) Comparison: EPA + DHA vs MUFA Intervention: 1.8 g/d fish oil capsules (Hoffman LaRoche, including ethyl esters of EPA and DHA, 0.76 g/d EPA, 0.54 g/d DHA) Control: 1.8 g/d olive oil capsules (Hoffman LaRoche, 73% oleic acid) Dose aim: increase 1.3 g/d EPA + DHA, 0.6% E n-3, 0.6% E PUFA Baseline PUFA not reported Compliance by biomarkers: while control group plasma and platelet DHA and EPA did not change, there were increases of 2%-8.3% in the intervention group. Plasma and red blood cell omega-3 fats were higher in intervention than control participants at all time points (P < 0.001). No data on total PUFA or LA plasma or red blood cell fats, and no TC reported

Raitt 2005 (Continued)

	Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, %E: not reported • PUFA intake, %E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • Sugars intake: not reported • Protein intake, % E: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported Inclusion basis: aims suggested total PUFA intake 0.6% E higher in intervention than control, a 10% increase on assumed 6% E from PUFA at baseline PUFA dose: 0.6% E Duration of intervention: 24 months (median 718 days)	
Outcomes	Main trial outcome: time to first episode of VT/VF Dropouts: 17 intervention, 26 control Available outcomes: deaths, CV death, MI, angina, revascularisation, atrial fibrillation, sudden cardiac death, cancer Response to contact: contact attempted but no response to date	
Notes	Trial funding: NIH and Hoffman LaRoche	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated block randomisation scheme"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participant blinding unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ICD traces were viewed by researchers blinded to allocation, "double blind placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Almost all participants were included in outcome assessment, well described

Raitt 2005 (Continued)

Selective reporting (reporting bias)	High risk	NCT registered in February 2000, trial carried out from February 1999 to January 2004. Most outcomes stated in registry entry reported, but quality of life missing
Attention bias	Low risk	Capsules were the only different interventions between arms, little opportunity for attention bias
Compliance	Unclear risk	No data on total PUFA or LA plasma or red blood cell fats, and no TC reported
Other bias	Low risk	None noted

Rose 1965

Methods	RCT, 2 arms, parallel (n6 LA vs MUFA), 24 months Summary risk of bias: moderate to high
Participants	People with ischaemic heart disease CVD risk: high N: 28 intervention, 26 control (analysed 15 intervention, 12 control) % male: not reported Mean age: 52.6 intervention, 55 control (no SDs) Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK Ethnicty: not reported
Interventions	Type: test oil provided (equivalent advice to both arms) Comparison: n-6 vs MUFA Intervention: 80 g/day corn oil to be taken in 3 equal doses at meal-times plus participants were instructed to avoid fried foods. Fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted: assuming 80% LA in corn oil, 64 g/d LA or 576 kcal/d or 28.8% E from LA Control: 80 g/day olive oil plus participants were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted. assuming 12% LA and 69% MUFA in olive oil, 9.6 g/d LA or 4.3% E LA and 55.2 g/d MUFA or 24.8% E Dose aim: +24.5% E from LA, -24.8% E MUFA Baseline PUFA: unclear Compliance using biomarkers: serum TC reduced, but not statistically significantly reduced in intervention compared to control (-0.49 mmol/L, 95% CI -1.34 to 0.36). No fatty acid biomarkers reported

Rose 1965 (Continued)

Compliance using dietary assessment: poor. Measured using questionnaire. Mean intake of oil in intervention was 595 kcal/d or 476 kcal/d LA or 23.8% E, in control 540 kcal/d or 3.2% E LA and 18.6% E MUFA, achieved: +20.6% E from LA, -18.6% E MUFA within the oils, unclear how diet altered • Energy intake: intervention 2070 kcal/d control 2045 kcal/d • Total fat intake: intervention 50 g/d + 595 kcal from oil or 1045 kcal/d or 52% E, control 45 g/d + 540 kcal from oil or 945 kcal/d or 47.3% E • SFA intake: not reported PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: +20.6% E (higher in intervention than control) • Trans fat intake: not reported (oils provided so not likely to be a problem) • MUFA intake: -18.6% E (lower in intervention than control) • CHO intake: intervention 189 g/d or 756 kcal/d or 37.8% E, control 216 g/d or 864 kcal/d or 43.2% E • Sugars intake: not reported • Protein intake: intervention 57 g/d or 228 kcal/d or 11.4% E, control 49 g/d or 196 kcal/d or 9.8% E • Alcohol intake: not reported Compliance by other methods: no others reported Inclusion basis: aim was to increase omega-6 fats, not total PUFA. Total PUFA not reported but LA dose so big that total PUFA must have been increased in intervention compared to control. Best estimate 20.6% E total PUFA dose, > 10% increase from baseline PUFA dose: according to questionnaire 20.6% E from LA, assume equivalent to 20.6% E from total PUFA Duration of intervention: 2 years Outcomes Main trial outcome: occurrence of infraction Dropouts: 6 intervention, 11 control?, details provided in table but unclear how many dropped out. Available outcomes: major CVD events, MI (fatal and non-fatal), sudden death, serum cholesterol Response to contact: not attempted as published in the 1960s Notes Trial funding: no details The trial had a 3rd control arm (no intervention), which has not been used here Risk of bias Bias Authors' judgement Support for judgement Random sequence generation (selection Low risk When a new participant was accepted for the trial a sealed envelope was opened con-

taining the allocation instructions. In the case of participants allocated to an oil group the instructions referred only to a code

number

Rose 1965 (Continued)

Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The physicians in charge knew which participants were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The electrocardiograms were assessed without the knowledge of the participant's treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	52% intervention, and 57% control remained in the trial after 24 months. However, the list of reasons and complications is provided
Selective reporting (reporting bias)	Unclear risk	No trial registry record or protocol found
Attention bias	Low risk	Oil provided to both groups, appeared similar
Compliance	Low risk	TC somewhat reduced in intervention compared to control (-0.49 mmol/L, 95% CI -1.34 to 0.36). No fatty acid biomarkers reported
Other bias	Low risk	None noted

Rossing 1996

Methods	RCT, parallel, (n3 EPA + DHA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	Adults with insulin-dependant diabetes mellitus, diabetic nephropathy and normal BP N: 18 intervention, 18 control (analysed, 17 intervention, 15 control) Level of risk for CVD: moderate Male: 64% intervention, 67% control Mean age (SD) years: 32 (7) intervention, 34 (10) control Age range: 18-55 years Smokers: 50% intervention, 47% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: insulin Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Denmark Ethnicity: not reported

Interventions	Type: supplement
	Comparison: fish oil vs olive oil
	Intervention: cod-liver oil emulsion (Pharma-Vinci A/S Denmark). EPA 2 g/d, DHA 2. 6 g/d, plus 24.1% SFA, 45.6% MUFA, 23.6% EPA + DHA, 6.7% other fats. Assumed
	total PUFA 4.6 g/d Control: olive oil emulsion (Pharma-Vinci A/S Denmark). 15.1% SFA, 76.9% MUFA, 8.0% other fats. Assumed total PUFA 0 g/d
	Dose aim: increase 4.6 g/d EPA + DHA, 2.1% E n-3, 2.1% E PUFA Baseline PUFA: unclear
	Compliance using biomarkers: assessed through omega-3 incorporation in platelets, and the paper reports significantly higher omega-3 levels in platelets at 12 months. EPA % was 0.59 (SE 0.07) in control, 2.70 (SE 0.29) in intervention arm latest reading. DHA % was 1.99 (SE0.13) control, 3.57 (SE 0.18) intervention (P < 0.001 between intervention and control for both). Total PUFA not reported. HOWEVER serum TC rose more in the intervention arm (+ 0.46 mmol/L) than control (+ 0.13 mmol/L) during
	Compliance using dietary assessment: poor. Unclear how measured, only protein re-
	ported • Energy intake: not reported
	Total fat intake: not reported
	SFA intake: not reported
	PUFA intake: not reported
	PUFA n-3 intake: not reported
	PUFA n-6 intake: not reported
	Trans fat intake: not reported
	MUFA intake: not reported
	CHO intake: not reported
	Sugars intake: not reported
	 Protein intake: intervention 1.07 g/kg/d (0.10), control 1.10 g/kg/d (0.07) Alcohol intake: not reported
	Compliance by other methods: no others reported
	Inclusion basis: aim was to increase omega-3 fats, not total PUFA. Total PUFA not
	reported but omega-3 dose rose by 2.1% E, so assume total PUFA did also as compared to MUFA. Best estimate 2.1% E total PUFA dose, more than 10% increase from assumed
	baseline of 6% E
	PUFA dose: intended dose only, 2.1% E
	Duration of intervention: 12 months
Outcomes	Main trial outcome: diabetic nephropathy Dropouts: 1 intervention, 3 control (though 3 further intervention participants are not included in all data) Available outcomes: mortality (nil), breast cancer, TC, LDL, systolic BP (TGs reported
	as medians so not used, albuminuria, fractional albumin clearance, transcapillary escape rate of albumin, prothrombin fragment reported as geometric means or medians, HbA1c, HDL and diastolic BP too different at baseline to include, glomerular filtration rate (GFR), plasminogen activator inhibitor-1 (PAI1), tissue plasminogen activator (TPA),

fibrinogen etc. not relevant) Trial author reply: yes

Rossing 1996 (Continued)

Notes	Trial funding: supported by The Danish Heart Association. Eskisol Fish oil and placebo oil emulsions were provided by Pharma-Vinci A/S, Frederiksvaerk, Denmark	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using "concealed randomization to receive either fish oil or olive oil in blocks of 4 according to their glomerular filtration rate."
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Active and placebo (olive oil) were given as emulsions with orange flavour. At the end patients were allowed to guess about treatment and ~50% were right" (from trial author response)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts similar between groups although relatively high for small sample size. 3 dropouts from fish oil and 1 from control due to side effects. ITT appears to have been given for albuminuria only
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention bias	Low risk	Time and attention appear to be the same. All participants were given dietary advice
Compliance	High risk	Total PUFA in body fractions not reported. However, serum TC rose more in the intervention arm (+0.46 mmol/L) than control (+0.13 mmol/L) during the trial
Other bias	Low risk	None noted

Simon 1997

Methods	RCT, parallel, (low fat with low PUFA vs usual diet), 24 months Summary risk of bias: moderate or high
Participants	Women with a high risk of breast cancer N: 98 intervention, 96 control (analysed 72 intervention: 75 control) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (SD): 46 (not reported) intervention, 46 (not reported) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported (those on statins excluded) Location: USA Ethenicity: white 89%, African American 9%, Hispanic 2%
Interventions	Type: dietary advice Comparison: reduced fat including PUFA (intervention) vs usual diet Intervention: aims total fat 15% E; methods biweekly individual dietetic appointments over 3 months followed by monthly individual or group appointments, including ed- ucation, goal setting, evaluation, feedback and self-monitoring. Intervention delivered face to face by a dietitian Control: aim usual diet, no stated intervention(s) Dose aim: unclear PUFA Baseline 7.7% E PUFA Compliance by biomarkers: no fatty acid biomarkers reported, TC reported in a sub- group and fell by 0.34 mmol/L in intervention and fell by 0.08 mmol/L in control over 1 year Compliance by dietary intake: assessed using 3-day 24-h recalls every 3 months, 1 year data reported • Energy intake, kcal/d: intervention 1570 (SE 47.0), control 1594 (SE 63.6) • Total fat intake, % E: intervention 17.6 (SD 5.8), control 33.8 (SD 7.4) • SFA intake, % E: intervention 6.0 (SD 3.0), control 12.1 (SD 5.2) • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake: not reported • MUFA intake: not reported • MUFA intake: not reported • Sugars intake: not reported • Protein intake: not reported • Protein intake: not reported • Alcohol intake: not reported Inclusion basis: no intention to increase total PUFA stated. Acheived total PUFA reduction of 6.7% E in intervention compared to control at 1 year, > 10% higher than baseline 7.7% E from total PUFA PUFA dose: -6.7% E PUFA

Simon 1997 (Continued)

	Compliance: dietary assessment Duration of intervention: 24 months (mean years in trial: control 1.8, intervention 1.7)
Outcomes	Main trial outcome: intervention feasibility Dropouts: unclear intervention, unclear control Available outcomes: TC, TG, LDL and HDL (2 deaths, but unclear in which arms, 8 cancer diagnosis but not clear in which arms), (weight, BMI, % body fat and waist-hip ratio reported but all too unbalanced at baseline to use) Trial author contact: Dr Simon confirmed that some deaths occurred (but not in which arms) and sent a further reference
Notes	Trial funding: Marilyn J Smith Fund, Harper-Grace Hospitals, the Wesley Foundation, National Cancer Institute, Karmanos Cancer Institute Core Grant, the United Foundation of Detroit Trialaim was to reduce total fat to 15% E (SFA not mentioned), but PUFA fat intake in the intervention group was significantly lower than in the control group Note: PUFA lower in intervention arm, so higher PUFA arm is the control

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by age and randomised (block size 2)
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly enough described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded (as given dietary advice or not), personnel unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts - unclear if any data missing
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention bias	High risk	Time and attention in the intervention group not mirrored in control
Compliance	High risk	No fatty acid biomarkers reported, TC reported in a subgroup and fell by 0.34 mmol/L in intervention and fell by 0.08 mmol/L in control over 1 year (but control group should have been higher in PUFA in

		this trial)	
Other bias	Low risk	None noted	
Sydney Diet-Heart 1978			
Methods	_	Sydney Diet-Heart Study RCT, 2 arm, parallel (n6 LA vs SFA), 4.3 years Summary risk of bias: low (as diet advice trial)	
Participants	Intervention: randomised 221, Mean years in trial: control 4.3, % male: 100 Age: mean intervention 48.7 (S Age range: 30-59 years Smokers: intervention 71.5%, of Hypertension: unclear Medications taken by ≥ 50% of Medications taken by 20%-499	CVD risk: high Control: randomised 237, analysed 221 at 2 years Intervention: randomised 221, analysed 205 at 2 years Mean years in trial: control 4.3, intervention 4.3 % male: 100 Age: mean intervention 48.7 (SD 6.8), control 49.1 (SD 6.5) Age range: 30-59 years Smokers: intervention 71.5%, control 68.8% Hypertension: unclear Medications taken by \geq 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia	
Interventions	Comparison: safflower oil and signal of SFA and MUFA) Control aims: reduction in energy to use PUFA margarine instead of Intervention aims: SFA 10% E, cholesterol < 300 mg/day thro (advised and tutored individual thereafter) Dose aim: increase 6.6% E PUB asseline n-6: unclear, 6.1% E FC Compliance by biomarkers: set to control (-0.30 mmol/L, 95% Compliance by dietary intake) • Energy intake, kcal/d: intervention of SFA intake, % E: intervention of the set	Control aims: reduction in energy if overweight, no other specific dietary advice, allowed to use PUFA margarine instead of butter (no specific dietary instruction, except re weight) Intervention aims: SFA 10% E, PUFA 15% E, reduction in energy if overweight, dietary cholesterol < 300 mg/day through provision of safflower oil and safflower margarine (advised and tutored individually, diet assessed 3 times in first year, twice annually thereafter) Dose aim: increase 6.6% E PUFA, most of which n6 Baseline n-6: unclear, 6.1% E PUFA, mostly n6 Compliance by biomarkers: serum TC significantly reduced in intervention compared to control (-0.30 mmol/L, 95% CI -0.51 to -0.09). No body fatty acid markers reported Compliance by dietary intake: good. From diet records, medians provided • Energy intake, kcal/d: intervention 2256, control 2194 • Total fat intake, % E: intervention -1.9, control -1.1 (reduction of 0.8% E total fat, not statistically significant) • SFA intake, % E: intervention -6.9, control -2.1 (reduction of 4.8% E SFA,	

statistically significant)

• PUFA n-3 intake: not reported

Sydney Diet-Heart 1978 (Continued)

	 PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake, % E: intervention -3.4, control -0.7 (reduction of 2.7% E MUFA, statistically significant) CHO intake, % E: intervention +1.4, control +0.1 (increase of 1.3% E CHO, not statistically significant) Sugars intake: not reported Protein intake, % E: intervention +0.4, control +1.2 (decrease of 0.8% E protein, not statistically significant) Alcohol intake, % E: intervention +0.7, control +1.7 (decrease of 1.0% E alcohol, not statistically significant) Compliance, other methods: not reported Inclusion basis: aimed to increase total PUFA intake as well as reduce SFA PUFA dose: 7.1% E PUFA (from dietary intake data) Duration of intervention: 2-7 years 		
Outcomes	Main trial outcomes: CV mortality and morbidity Dropouts: unclear, probably 16 dropouts in each arm, but participants were included from 2-7 years Available outcomes: mortality, TC, TG Response to contact: yes, further data provided		
Notes	Trial funding: Life Insurance Medical Research Fund of Australia and New Zealand		
Risk of bias	Risk of bias		
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers generated by a research assistant and was concealed until after medical evaluations and testing at baseline were completed"	
Allocation concealment (selection bias)	Low risk	As above	
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where participants need to make their own dietary changes	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Initially masked to group assignment (though success of blinding not checked)	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Survival analysis used	
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located	

Sydney Diet-Heart 1978 (Continued)

Attention bias	High risk	Different levels of dietary support (non-dietary aspects were equivalent)
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.30 mmol/L, 95% CI -0.51 to -0.09). No body fatty acid markers reported
Other bias	Low risk	None noted

Veterans Admin 1969

veterans Admin 1969	
Methods	Veterans Administration Trial RCT, 2 arms, parallel (n6 LA vs SFA), up to 8 years Summary risk of bias: moderate to high
Participants	Men living at the Veterans Administration Centre CVD risk: low Control: randomised 422, analysed 422 Intervention: randomised 424, analysed 424 Mean years in trial: control 3.7, intervention 3.7 % male: 100 Age: mean control 65.6, intervention 65.4 Age range: all 54-88 years Smokers: intervention 283, control 279 (unknown intervention 41, control 58) Hypertension: unclear Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: digitalis, diuretics, oestrogens, corticoids, androgens, coumarins, nicotinic acid Location: USA Ethnicity: white 90%, black 7%, Asian 1%, Hispanic 1%, other 1%
Interventions	Type: diet provided (residential institution) Comparison: corn, soybean, safflower and cottonseed oils (n-6) vs usual institutional diet Control aims: provided, total fat 40% E (whole diet provided) Intervention aims: total fat 40% E, 2/3 of SFA replaced by unsaturated fats (from corn, soybean, safflower and cottonseed oils), dietary cholesterol reduced (whole diet provided) Dose aim: 2/3 of baseline SFA is increase of ~12%E PUFA Baseline n-6: 4% E LA, control arm 4.8% E PUFA Compliance by biomarkers: subcutaneous 18:2 + 18:3 11.7% fat at baseline, rising to 12.8% fat in control and 34.8% fat in intervention (after "prolonged" adherence to diet). Serum TC reduced, but not statistically significantly in intervention compared to control (-0.37 mmol/L, 95% CI -0.77 to 0.03) Compliance by dietary intake: unclear, checked using coloured tickets to assess dining room attendance - described as 49% in intervention and 56% in controls. Laboratory analysis of the mean of over 400 weekly collections of diet provided:

Veterans Admin 1969 (Continued)

	(4.8% E) in control and 43% in intervention PUFA n-3 intake, % E: not reported PUFA n-6 intake, % E: intervention Trans fat intake: not reported MUFA intake, % E: intervention 14. CHO intake: not reported Sugars intake: not reported Protein intake, % E: intervention 15. reported Alcohol intake: not reported Compliance by other methods: no others in Inclusion basis: aim was to increase unsat	ontrol 18.5 (decrease 10.2% E SFA) in in graph as 18:2 + 18:3 –12% of dietary fat ion (17.2% E), increase 12.4% E 16.1, control 4.4 (increase 11.7% E LA) 6, control 17.1 (decrease 2.5% E MUFAs) 6 (SD not reported), control 15.4 (SD not reported urated fats, not total PUFA. Total PUFA not ate), > 10% increase from baseline of ~5% E
Outcomes	Main trial outcomes: mortality, heart disease Dropouts: intervention 117, control 58 withdrawals over whole trial, a few participants were involved for up to 8-9 years Available outcomes: mortality, CV mortality (sudden death, definite MI, definite stroke, angina, PAD events), cancer deaths, cancer diagnoses, stroke, non-fatal MI, total MI, CHD deaths (fatal MI and sudden death due to CHD), CHD events (any MI or sudden death due to CHD), some data on TC, but no variance info Response to contact: attempted but no author contact established (trial published in 1969)	
Notes	Trial dates: recruitment 1959-1967 Trial funding: mainly US Public Health Service, Los Angeles County Heart Assoc, Arthur Dodd Fuller Assoc, but Corn Products Co (provided Corn oil and margarine), National Soybean Processors Assoc (provided soybean oil), Pitman-Moore Co (provided margarine), Frozen Desserts Co (imitation ice cream). All trial authors worked for academic or health institutions	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers used"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Institution provided diet in a masked fashion

• Energy intake, kcal/d: intervention 2496, control 2496

All outcomes

Veterans Admin 1969 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physician knowledge of allocation was assessed and found not much better than random
Incomplete outcome data (attrition bias) All outcomes	Low risk	All followed up via Veterans Admin system
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	Low risk	Appeared equivalent, diet provided to both arms
Compliance	Low risk	Subcutaneous 18:2 + 18:3 11.7% fat at baseline, rising to 12.8% fat in control and 34.8% fat in intervention (after "prolonged" adherence to diet). TC reduced, but not statistically significantly in intervention compared to control (-0.37 mmol/ L, 95% CI -0.77 to 0.03)
Other bias	Low risk	None found

Vijayakumar 2014

Methods	RCT, 2 arms, parallel (n6 LA vs SFA), 2 years Summary risk of bias: moderate to high
Participants	People with stable coronary artery disease CVD risk: high N: intervention (sunflower oil): 100 randomised, analysed at 2 years 94; control (coconut oil): 100 randomised, analysed at 2 years 96 Mean years in trial: 2 % male: intervention 92.9%, control 93.9% Age, mean (SD) years: intervention 59.0 (8.9), control 59.0 (8.4) Age range: unclear Smokers, ex: intervention 57.1%, control 54.1% Hypertension: intervention 55.1%, control 58.2% Medications taken by ≥ 50% of those in the control group: statins Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: fibrates, nicotinic acid Location: India Ethnicity: not reported
Interventions	Type: food (cooking oil) provided Comparison: sunflower oil (n6) vs coconut oil (SFA) Intervention aims: whole family to use branded sunflower oil for cooking (15% E provided in form of sunflower oil, ~66% PUFA) Control aims: whole family to use branded coconut oil for cooking (15% E provided in

Vijayakumar 2014 (Continued)

	vention compared to control (-0.06 mmol/I in control, fell slightly in intervention. No Compliance by dietary intake: unclear. Re used to monitor intake, but results not provous Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported • Inclusion basis: did not aim to increase	eports that 7-day recall and diet diaries were
Outcomes	Main trial outcome: CV risk factors Dropouts: intervention 6 lost, control 4 lost Available outcomes: lipids, death, revascularisation, (glycaemic control, weight, BMI available but unbalanced at baseline) Response to contact: author replied and provided additional outcome data	
Notes	Trial funding: coconut development board, Amrita Institute of Medical Science and Research. Sponsors had no role in trial design or analysis	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with 5 blocks of 40
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unlikely as participants and their families used branded oils

Vijayakumar 2014 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% withdrawals. Clear, with reasons
Selective reporting (reporting bias)	Unclear risk	Unclear, no protocol or trials register entry found
Attention bias	Low risk	Appeared equivalent
Compliance	Low risk	TC reduced in intervention compared to control (-0.06 mmol/L, 95% CI -0.22 to 0.34, rose slightly in control, fell slightly in intervention). No biomarker data reported
Other bias	Low risk	None noted

WAHA - Ros 2016

Methods	The Walnut and Healthy Aging Study (WAHA) 2 arms, parallel RCT (n3 ALA vs mixed fats, ALA provided as walnuts), 2 years Summary risk of bias: moderate to high
Participants	Middle-aged, healthy adults N: 362 intervention, 346 control (only preliminary data on 260 intervention, and 254 control available) Level of risk for CVD: low Male: 32.6% intervention, 31.5% control Mean age (SD): 69.4 (3.8) intervention, 68.9 (3.5) control Age range: 63-79 (inclusion criteria) Smokers: 4.4% intervention, 1.2% control Hypertension: 52.8% intervention, 52.9% control Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Spain and USA Ethnicity: not reported
Interventions	Type: supplement (food) Comparison: ALA vs nil Intervention: 15% of daily energy intake as walnuts. The estimated amount of walnuts ranged from 1-2 oz/d (-30-60 g/day). Sachets for daily consumption containing 30, 45, or 60 g of raw, pieced walnuts were provided as 8-week allotments to be eaten daily, preferably as the raw product, either as a snack or by incorporating them into shakes, yogurts, cereals, or salads. To improve participants' compliance, 1- kg extra walnut allowances were provided every 2 months to take into account family needs

Control: usual diet without walnuts

Compliance: assessed by dietitians through Food Frequency Questionnaires, recount of empty packages, and changes in fatty acids concentrations. 95% consumed ≥ 1 oz./d. The proportion of α -linolenic acid in red blood cell counts increased in the walnut group by 0.162% (95% CI 0.143 to 0.181) and in the control group by 0.015% (95% CI -0.005 to 0.035) (P < 0.001)

Dose aim: increase (assuming 10% E in walnuts is ALA) 1.5% E n3 ALA. 45 g walnut gives ~65% or 29.3 g oil, of which ~68% PUFA, 19.9 g/d oil, 9% E PUFA Baseline PUFA: unclear, control 7.9% E PUFA

Compliance by biomarkers: erythrocyte ALA increased by 28% in intervention, reduced by 17% in control (in a subsample of participants, percentage of total fatty acids in red blood cells also increased in intervention group compared to control, no other erythrocyte fatty acids reported. TC fell by 0.19 mmol/L (SD 0.04) in intervention, and by 0.01 mmol/L (SD 0.04) in control to 1 year

Compliance by dietary intake: mean of five, 24-h diet recalls over 2 years of trial

- Energy intake, kcal: intervention 1821 (SD not reported), control 1593 (SD not reported)
- Total fat intake, % E: intervention 41.5 (SD not reported), control 35.6 (SD not reported) (increase of 5.9% E)
- SFA intake, % E: intervention 10.9 (SD not reported), control 11.9 (SD not reported) (reduction of 1.0%E SFA)
- PUFA intake, % E: intervention 15.3 (SD not reported), control 7.9 (SD not reported) (increase of 7.4% E PUFA)
- PUFA n-3 intake, % E: intervention 2.5 (SD not reported), control 0.9 (SD not reported) (increase of 1.6% E)
- PUFA n-6 intake, % E: intervention 12.9 (SD not reported), control 7.0 (SD not reported (increase of 5.9% E)
 - Trans fat intake: not reported
- MUFA intake, % E: intervention 12.4 (SD not reported), control 12.4 (SD not reported (0% E)
- CHO intake, % E: intervention 44.8 (SD NRnot reported, control 48.2 (SD not reported) (reduction of 3.4% E)
 - Sugars intake: not reported
- Protein intake, % E: intervention 15.4 (SD not reported), control 16.3 (SD not reported) (decrease of 0.9% E)
 - Alcohol intake, not reported
- (Also slightly higher intakes of most micronutrients reported)

Compliance, other methods: assessed by dietitians through Food Frequency Questionnaires and recount of empty packages, 95% consumed $\geq 28g/d$

Inclusion basis: aimed to increase walnuts, not total PUFA. Resulted in increase of 7. 4% E total PUFA

PUFA dose: 7.4% E PUFA (from dietary intake data)

Duration of intervention: 2 years

Outcomes

Main trial outcome: change in cognitive decline (results not yet published)

Dropouts: 36 intervention, 21 control (after 1 year)

Available outcomes: CVD events, cancers, lipids (for TG and HDL only data states "no between diet differences were observed"), weight (waist circumference was provided but without variance, abstract stated that "there were no significant changes in body fat and

WAHA - Ros 2016 (Continued)

	waist-to-hip ratio over time and between the two groups"). Cognitive, ophthalmological, inflammatory markers, glycaemic status and other outcomes are not yet available. Response to contact: author replied and provided additional outcome and methodological data	
Notes	Trial funding: funding was provided by the Calfornia Walnut Commission The 2-year results as well the full 1-year results are yet to be published	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized to either the control or walnut group using a computerized ran- dom number table with stratification by center, sex, and age range. Couples entering the trial were treated as one number and were randomized into the same group"
Allocation concealment (selection bias)	Low risk	Author reply stated "Baseline subject data was collected before randomization. Randomization was done by the clinician, pressing the key on the computer"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind. Quote: "An unavoidable limitation of the study is not being able to blind participants to the intervention since it consists of a whole food" Rajaram 2017
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind. Author reply stated "Study personnel not in contact with the subjects were blind to the treatment assignment. So (lab technicians, ophthalmology technician, neuro cognitive testers) were not aware of the treatment assignment. Of course clinicians who were visited by subjects every two months, knew the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	38/362 dropouts in intervention group = 10.5%. 34/346 dropouts in control group = 9.8%. Similar dropout in groups over 2 years
Selective reporting (reporting bias)	Unclear risk	Although prospectively registered, no full results paper published - results from conference abstracts and papers only report some secondary outcomes and dietary data

WAHA - Ros 2016 (Continued)

Attention bias	Unclear risk	Not enough detail to assess
Compliance	Low risk	Erythrocyte ALA increased by 28% in intervention, reduced by 17% in control (in a subsample of participants), percentage of total fatty acids in red blood cells also increased in intervention group compared to control, no other erythrocyte fatty acids reported. TC fell by 0.19 mmol/L (SD 0.04) in intervention, and by 0.01 mmol/L (SD 0.04) in control to 1 year
Other bias	Low risk	None noted

WELCOME 2015

Methods	RCT, parallel, (n3 EPA + DHA vs MUFA), 15-18 months Summary risk of bias: low
Participants	Patients with NAFLD N: 51 intervention, 52 control (analysed, 47 intervention, 48 control) Level of risk for CVD: moderate Male: 49% intervention, 67% control Mean age (SD): 48.6 (11.1) intervention, 54 (9.6) control Age range: not reported (18-75 inclusion criteria) Smokers: 14.3% intervention, 11.8% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: lipid-lowering drugs Medications taken by 20%-49% of those in the control group: antihypertensives, metformin (data not provided by group) Medications taken by some, but < 20% of the control group: none reported Location: UK Ethenicity: not reported
Interventions	Type: supplement (Omacor capsules) Comparison: DHA + EPA vs MUFA Intervention: 4 g Omacor/d (providing 1.84 g EPA, 1.52 g DHA as ethyl esters)), 3.36 g/d EPA + DHA Control: 4 g olive oil capsules/d (providing; ALA 1%, oleic acid 67%, palmitic acid 15%, stearic acid 2%, n-6 fat: 15%), 0.64 g/d PUFA Dose aim: increase 2.72 g/d PUFA, 1.22% E PUFA Baseline PUFA unclear Compliance by biomarkers: erythrocyte EPA + DHA both increased in intervention, not in control (EPA% 1.0%, SD 0.2% in control vs 2.4% SD 1.8% in intervention at latest point, DHA% 5.0 SD 1.0 in control, 7.1% SD 1.3% in intervention), no other fatty acids reported. TC remained 4.8 mmol/L in control but fell by 0.2 mmol/L to 4.7 mmol/L in intervention at 15-18 months Compliance by dietary intake: not reported

WELCOME 2015 (Continued)

	 Energy intake: not reported Total fat intake: not reported SFA intake: not reported PUFA intake: not reported PUFA n-3 intake: not reported PUFA n-6 intake: not reported Trans fat intake: not reported MUFA intake: not reported CHO intake: not reported Sugars intake: not reported Protein intake: not reported Alcohol intake: not reported Alcohol intake: not reported Tompliance, other methods: assessed by recording the returned unused capsules, but results not reported Inclusion basis: no intention to increase total PUFA stated. Planned total PUFA increase 2.72 g/d PUFA, 1.22% E PUFA, > 10% higher than assumed 6% E from total PUFA at baseline. Confirmed by TC fall in intervention, no other biomarker or intake data PUFA dose: 1.22%E PUFA Duration of intervention: 15-18 months
Outcomes	Main trial outcome: changes in mean liver fat %, changes in 2 liver fibrosis scores, change in serum biomarkers Dropouts: 4 intervention, 4 control Available outcomes: weight, BMI, lipids, BP, glucose, insulin sensitivity, body fat measures, liver enzymes, HbA1c, serum n-3 fatty acids, trial authors provided details of diabetes diagnoses, % body fat, BP and carotid intima media thickness Response to contact: yes
Notes	Trial funding: Omacor and placebo were provided by Pronova Biopharma through Abbott Laboratories, Southampton, UK. This work was supported by a National Institute for Health Research (NIHR) Southampton Biomedical Research Unit grant and by a Diabetes UK Allied Health Research training fellowship awarded to KGM (Diabetes UK. BDA 09/ 0003937). CDB, PCC and ES were supported in part by the NIHR Southampton Biomedical Research Centre (McCormick-2015, p9; see WELCOME 2015)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were block randomised by an independent clinical trials pharmacist randomised according to standardised procedures (computerised block randomisation) by a research pharmacist at University Hospital Southampton NHS Foundation Trust. Simple randomisation in blocks of 4

WELCOME 2015 (Continued)

Allocation concealment (selection bias)	Low risk	Only the clinical trials pharmacist was unblinded, and randomisation group allocation was concealed from all trial members throughout the trial. (McCormick-2015, p2)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states that only the clinical trials pharmacist was unblinded, and randomisation group allocation was concealed from all trial members throughout the trial. However, the trial register record states "single blind (investigator)". Although the capsules were identical, no information provided as to their smell and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The ITT included all participants randomised who had complete data (baseline and end-of-trial measurements), regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment allocation, or never treated). (Scorletti 2014, p4; see WELCOME 2015)
Selective reporting (reporting bias)	Unclear risk	Prospectively registered September 2008, trial start September 2009, end February 2017. Outcome data for cardiac function not yet published (may be ongoing as trial only recently completed), though other CV measures reported
Attention bias	Low risk	Both groups had the same attention
Compliance	Low risk	Erythrocyte EPA + DHA both increased in intervention, not in control (EPA% 1.0%, SD 0.2% in control vs 2.4% SD 1.8% in intervention at latest point, DHA% 5.0 SD 1.0 in control, 7.1% SD 1.3% in intervention), no other fatty acids reported. TC remained 4.8 mmol/L in control but fell by 0.2 mmol/L to 4.7 mmol/L in intervention at 15-18 months
Other bias	Low risk	None noted

WINS 2006

Methods	Women's Intervention Nutrition Study (WINS) RCT, parallel, (reduced fat with reduced PUFA vs usual diet), 60 months Summary risk of bias: low (as diet advice trial)
Participants	Women with localised resected breast cancer N: 975 intervention, 1462 control (analysed 975 int, 1462 cont) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (95% CI): 58.6 (44.4-72.8) intervention, 58.5 (43.6-73.4) control Age range: not reported, all postmenopausal Smokers: 49.9% intervention, 48.7% control never smokers Hypertension: not reported Medications taken by ≥ 50% of those in the control group: menopausal hormone therapy (65.3% intervention, 64.0% control), tamoxifen (47.7% tamoxifen alone, 38.5% tamoxifen plus chemotherapy in intervention, 47.4% and 38.0% respectively in control), all were on chemotherapy, most on radiotherapy Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: 85% white, 5% black, 4% Hispanic, 5% Asian or Pacific Islander, < 1% American Indian or unknown (no outcome data based on ethnicity)
Interventions	Type: dietary advice Comparison: reduced fat intake (with reduced PUFA) vs usual diet Intervention: aims total fat 15%-20% E; methods 8 biweekly individual dietetic sessions plus 3-monthly contact and optional monthly group sessions, incorporating individual fat gram goals, social cognitive theory, self-monitoring, goal setting, modelling, social support and relapse prevention and management. Intervention was delivered face to face individually by trained dietitian Control: aims minimal nutritional counselling focused on nutritional adequacy; methods one baseline dietetic session plus 3-monthly sessions Dose aim: unclear PUFA Baseline 5.4% E PUFA Compliance by biomarkers: no fatty acid biomarkers reported, TC reported but only in a subgroup (N = 18 at 2 years) and unbalanced at baseline so not used in analyses, little change but TC fell by 6 mg/dL in intervention and increased by 0.8 mg/dL in control over 2 years Compliance by dietary intake: assessed using unannounced phone calls over several days, 1-year data reported apart from protein and carbohydrate which were 6-month data • Energy intake, MJ/d: intervention 7.3 (SD 1.8), control 7.7 (SD 1.9) • Total fat intake, % E: intervention 20.3 (SD 8.1), control 29.2 (SD 7.4) • SFA intake: intervention 6.4 (SD 0.14 (4.4)), control 9.8 (SD 0.15 (5.7)) • PUFA intake: intervention 4.5 (SD 0.09 (2.8)), control 6.4 (SD 0.10 (3.8)) • PUFA n-6 intake: not reported • Trans fat intake: not reported

WINS 2006 (Continued)

	 Sugars intake: not reported Protein intake, % E: intervention 19.1 (SD 5.2), control 17.6 (SD 4.1) Alcohol intake: intervention 5% E (SD 6), control 4% E (SD 6) Compliance, other methods: not reported Inclusion basis: no intention to increase total PUFA stated. Acheived total PUFA reduction of 1.9% E in intervention compared to control at 1 year, > 10% higher than baseline 5.4% E from total PUFA PUFA dose: -1.9% E PUFA Duration of intervention: 60 months
Outcomes	Main trial outcome: dietary fat intake, TC, weight and waist Dropouts: 45 lost to follow-up, 170 discontinued intervention, 66 lost and 106 discontinued control Available outcomes: all-cause mortality, cancer diagnoses (including recurrences), new breast cancer diagnoses, weight, BMI (TC, TG, HDL, insulin provided in tiny subgroup - 9 participants in each group at 2 years - and unbalanced at baseline, not useable) Author contact: limited information received
Notes	Trial funding: National Cancer Institute, Breast Cancer Research Foundation, American Institute for Cancer Research *SDs appear incorrect, probably SEs? NOTE: control arm is the arm higher in PUFA, intervention arm lower in PUFA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS
Allocation concealment (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not for dietary advice and participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes assessed by the blinded outcome committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All assessed
Selective reporting (reporting bias)	Low risk	Outcomes stated in protocol all appear to have been published

WINS 2006 (Continued)

Attention bias	High risk	Intervention group appear to have received more time and attention
Compliance	Unclear risk	No fatty acid biomarkers reported, TC reported but only in a subgroup (n = 18 at 2 years) and unbalanced at baseline so not used in analyses, little change but TC fell by 6 mg/dL in intervention and increased by 0.8 mg/dL in control over 2 years (note, control group should be higher in PUFA in this trial). Overall changes not reported
Other bias	Low risk	None noted

AA: arachidonic acid; ACEi: angiotensin-converting-enzyme inhibitor; AF: atrial fibrillation; ALA: alpha-linolenic acid (a plant-based omega-3 fat); ARB: Angiotensin II receptor blockers; BMD: bone mineral density; BMI: body mass index (weight in kg divided by height in m squared); BP: blood pressure; Ca: calcium; CAD: coronary artery disease; CHO: carbohydrate; CLO: cod-liver oil; CRP: C-reactive protein; CV: cardiovascular; CVD: cardiovascular diseases; DHA: docosahexaenoic acid (a fish-based omega-3 polyunsaturated fatty acid); DPA: docosapentaenoic acid (a fish-based omega-3 polyunsaturated fatty acid); E: energy; EPA: eicosapentaenoic acid (a fish-based omega-3 polyunsaturated fatty acid); FMD: fibromuscular dysplasia; GLA: gamma linolenic acid (an omega-6 polyunsaturated fatty acid); HDL: high density lipoprotein (a fraction of TC, measured in human blood); ICD: implanted cardioverter defibrillator; ITT: intention to treat analysis; IQR: interquartile range; kcal: calories; LDL: low density lipoprotein (a fraction of TC, measured in human blood); LA: linoleic acid (an omega-6 polyunsaturated fatty acid); MD: mean difference; MI: myocardial infarction; MUFA: monounsaturated fatty acid or monounsaturated fat; IQR: interquartile range; N: number or participants; NAFLD: non-alcoholic fatty liver disease; NSAIDs: nonsteroidal antiflammatory drugs; P: P value; PCI: percutaneous coronary intervention; PUFA: polyunsaturated fatty acid; P/S: polyunsaturated to saturated fatty acid ratio; PAD: peripheral arterial disease; QoL: quality of life; RCT: randomised controlled trial; SCD: sudden cardiac death; SD: standard deviation; SE: standard error; SFA: saturated fatty acid or saturated fat; SO: seal oil; TC: total cholesterol (measured in human blood); TG: triglycerides (measured in human blood); VF: ventricular fibrillation; VT: ventricular tachycardia

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
ADCS-Quinn 2010	Compared DHA vs omega-6, no intention to increase total PUFA. Intervention 1.02 g/d algalderived DHA compared to 2 g of soy or corn oil. Biggest difference would be 1 g/d total PUFA, 0.45% E, < 10% change from assumed 6% E baseline PUFA
AFFORD 2014	Aim was to assess effects of high-dose fish oils, compared EPA + DHA (1.6 g/d EPA + 0.8 g/d DHA) vs omega-6 safflower oil (4 g/d, ~80% LA). Assumed 2.4 g/d or 1.08% E omega-3 in intervention, 3.2 g/d or 1.44% E omega-6 fats in control, difference 0.8 g/d or 0.36% E total PUFA. This was < 10% increase from assumed baseline of 6% E total PUFA. No biomarker, lipid or dietary intake data to support

AlphaOmega - EPA+DHA	Aim was to increase omega-3 fats. Margarine composition data - summing LA, ALA, EPA, DPA and DHA total PUFA suggested dose in EPA + DHA margarine (compared to placebo) was 3.8% E. As planned intake was 20 g/d, intake was 0.76 g/d total PUFA, or 0.3% E from total PUFA. Total PUFA in ALA + EPA + DHA (compared to ALA margarine) was 0.7% E, or 0.14 g/d total PUFA, 0.06%E total PUFA. These were both < 10% higher than assumed 6% E from PUFA at baseline. TC levels did not alter by intervention
AREDS2 2014	Aimed to increase omega-3 fats, compared EPA + DHA (350 mg/d DHA plus 650 mg/d EPA) vs nil. Intended increase 1.0 g/d, 0.5% E n-3, assume 0.5% E PUFA (< 10% increase from assumed 6% E PUFA at baseline). No biomarker, lipid or dietary intake data to support or refute
ASCEND	Ongoing trial. Intervention omega-3 (1 g/d: 0.41 g EPA, 0.34 g DHA) vs olive oil placebo (plus or minus aspirin). Dose appears < 1.33 g/d total PUFA, < 0.6% E PUFA, so excluded
Azadbakht 2007	Weight reduction goals as well as fat modification, multifactorial
Baldassarre 2006	Aim to increase omega-3. Compared LCn3 (1.8 g/d EPA + DHA, 0.12 g LA, 1.92 g/d PUFA) vs MUFA (~20% LA or 1.2 g/d PUFA). Dose 0.72 g/d PUFA, 0.3% E total PUFA, < 10% of baseline assumed 6% E PUFA. No biomarker data except on EPA + DHA, no dietary intake data presented, no postbaseline TC data but LDL increased in intervention arm and remained static in control
Berson 2004	DHA vs omega-6, there appeared to be roughly the same amount of PUFA in both intervention and control supplements, but exact composition unclear $(1.2g/d\ DHA\ plus\ 1.8\ g\ vegetable\ oil\ vs\ 3\ g/d\ mixed\ soy\ and\ corn\ oils\ (half\ each).$ Appeared to be < 10% difference in total PUFA between arms
Caldwell 2011	Compared EPA + DHA vs omega-6, did not report intention to increase total PUFA. Intervention 2.1 g/d n3 (1050 mg EPA, 750 mg DHA and 300 mg other n3), control 3 g/d soybean oil (approx 60% PUFA plus 8% fish oil, 2.04 g/d), PUFA Dose 0.06 g/d, 0.03% E PUFA, < 10% increase from assumed 6% E baseline. Only erythrocyte fatty acid ratio reported, no TC or dietary intake data reported
DART 2 - Burr 2003	Aimed to increase oily fish intake or update of fish oil capsules. No PUFA aim, no PUFA biomarkers (though plasma EPA rose 1.23 mg/dl in intervention, fell 0.16 mg/dL in control over 6 months) or intake data reported. Aim for those on capsules was increase 0.5 g/d EPA + DHA, 0.2% E n-3, 0.2% E PUFA. < 10% increase from assumed 6% E from PUFA baseline
DART fish Burr 1989	EPA + DHA vs nil, aimed to increase omega-3 intake by increasing fatty fish intake. No total PUFA goals or data on intake, serum fatty acids or serum cholesterol. Dose aim increase 0.5 g/d EPA + DHA, 0.2% E n-3, 0.2% E PUFA. < 10% increase over assumed 6% E PUFA at baseline
Derosa 2016	Compared EPA + DHA vs filler (non-fat), no intention to increase total PUFA. Omega-3 dose unclear, states intention in intervention of 3 x 1 g capsule/d n-3 PUFAs (ethylic esters, each 1-g capsule of n-3 PUFAs contains highly concentrated ethyl esters of omega-3 fatty acids, primarily EPA, and DHA in the proportion of 0.9-1.5), compared to placebo of "sucrose, mannitol and mineral salts magnesium stearate and silicon dioxide, used as anti-caking agents". Both groups were given diet and exercise advice. No biomarker or intake data provided on omega-3 or total PUFAs, TC not significantly different between arms. If omega-3 dose was 1 g/d, or 0.45% E this

	would be < 10% E increase from an assumed baseline of 6% E
Deslypere 1992	Compared LCN3 vs MUFA, no intention to increase total PUFA. Intended dose appeared relevant for 6 and 6 capsule arms (increase 1.12 g/d EPA + DHA, 0.5% E n-3, 0.5% E PUFA or 2.24g/d EPA + DHA, 1.0% E n-3, 1.0% E PUFA or 3.4 g/d EPA + DHA, 1.5% E n-3, 1.5% E PUFA) but total PUFA intake appeared equal in all arms (subtracting SFA and MUFA from total fat), and erythrocyte membrane fatty acids similar in all arms (summing EPA, DHA, DPA, LA and AA, 30.6% fatty acids for 9-capsule arm, 30.5% 6 capsules, 29.9% 3 capsules and 29.1% fatty acids in control arm. Did not appear to be > 10% increase in total PUFA between intervention and control arms
DISAF - Harrison 2005	Compared EPA + DHA vs nil, did not aim to increase total PUFA. Aimed to increase 1.4 g/d EPA + DHA, 0.6% E n-3, this equates to 0.6% E PUFA in intervention arm, no change in control. While red cell membrane EPA and DHA increased in the intervention group, not in control, AA was reported as falling in intervention. PUFA (summed EPA + DHA and AA was 17.8% in intervention, 17.6% in control. Other PUFAs and TC not reported. Difference in total PUFA between intervention and control < 10% control
DO Health	Ongoing trial. Intervention omega-3 (1 g/d, ratio EPA:DHA = 1:2) vs placebo capsules (plus or minus vitamin D3 and strength home exercise). Dose of total PUFA appears < 1.33 g/d, $< 0.6\%$ E PUFA, so excluded
DO IT - Einvik 2010	Compared EPA + DHA vs omega-6, no aim to increase total PUFA. Intervention aim 2.4 g/d of omega-3 PUFA (EPA + DHA 1.32 g/d, assume 1.08 g/d ALA or other omega-3) vs corn oil (2.24 g/d LA). 2.4 g/d omega-3, 1.1% E n3 vs 2.24 g/d LA or 1.0% E LA, PUFA dose 0.1% E. < 10% increase from assumed 6% E baseline. Serum fatty acids suggest < 10% more total PUFA in both intervention arms than controls, no difference in TC between arms
DO IT 2006	Dietary advice arm provided multifactorial dietary advice, while the supplementary arm was a specifically omega-3 intervention (so included in the omega-3 review)
EPE-A study 2014	Compared: high EPA vs low EPA vs placebo (contents not reported). PUFA content of placebo unknown. High EPA (increase 2.7 g/d EPA + DHA, 1.2% E omega-3, 1.2% E PUFA) vs low EPA (increase 1.8 g/d EPA + DHA, 0.8% E omega-3, 0.8% E PUFA), PUFA dose 0.4% E, < 10% increase from assumed 6% E at baseline. Serum EPA to AA (0.57 in high dose, 0.40 in low dose, 0.09 in control), TC rose by 8 mg/dL in control, by 4 mg/dL in high dose and by 3 mg/dL in moderate dose)
Erdogan 2007	Intervention and control group contents unclear, so unclear if more PUFA vs less
Finnish Mental Hosp 1972	Not randomised (cluster-randomised, but < 6 clusters)
FLAX-PAD 2013	Compared ALA (in milled flaxseed) vs mixed dietary oils (composition unclear). No intention to increase total PUFA. Quantity of ALA and other PUFA unclear in both arms. Plasma levels of enterolignans and ALA rose in ALA arm, no details for control. No suggestion that total PUFA intake was higher in either arm, exclude
FORWARD 2013	Compared EPA + DHA vs MUFA, no aim to increase total PUFA. Intervention provided 0.86 g/d EPA + DHA, 0.4% E n-3, 0.4% E PUFA, control provided 1 g/d olive oil, or 0.2 g/d LA. Total

	PUFA dose 0.66 g/d PUFA, 0.3% E, < 10% higher than assumed 6% E PUFA baseline
FOSTAR 2016	Compared high EPA + DHA vs low EPA + DHA plus ALA. Intervention fruit juice mixed with fish oil supplement (18% EPA, 12% DHA, 4.5 g/day total omega-3), control 15 mL Sunola oil/d (fish oil 2 mL plus 13 mL canola oil, omega-3 \leq 0.45 g EPA + DHA plus 3.9 g/d PUFA in canola, 4.4 g/d PUFA). ~0.1 g/d PUFA more in intervention, < 10% more than assumed 6% E PUFA at baseline
Franzen 1993	Compared EPA + DHA vs MUFA. No intention to increase total PUFA stated but increased omega-3 (20% EPA, 15% DHA, 3.15 g/day total omega-3) vs increased olive oil (6.3 g/day MUFA, 1.35 g/day SFA, 1.35 g/d total omega-6 fat). This suggests increase 1.8 g/d PUFA, 0.8% E PUFA, but serum fatty acids (summing EPA, DHA, ALA, LA, AA, DPA) suggested higher total PUFA in control (182 mg/dL PUFA in intervention, 195 mg/dL in control). However, TC rose more in control than intervention. Change in total PUFA unclear, exclude
Gill 2012	Compared omega-3 with placebo (unclear what), no aim to increase total PUFA. Control group contents unclear, so unclear if more PUFA vs less, no biomarker or intake data, TC reported only as "no significant change". Change in total PUFA unclear, exclude
GISSI-HF 2008	Compared EPA + DHA vs MUFA, no aim to increase total PUFA. Intervention increased 1 g/d omega-3, 1 g/d olive oil, or 0.2 g/d LA in control, dose 0.8 g/d total PUFA, 0.36% E PUFA, < 10% increase from assumed 6% E PUFA. Fatty acid status did not provide total PUFA or any omega-6 PUFAs, TC data provided for intervention but not control
GISSI-P 1999	Compared EPA + DHA vs nil, no aim to increase total PUFA. Intervention dose 0.86 g/d EPA + DHA, 0.4% E n-3, 0.4% E PUFA, < 10% increase from assumed 6% E PUFA. No biomarker or intake data, TC appeared to rise slightly more in intervention than control arms to 6 months
JELIS 2007	Compared EPA fats with nil, no intention to increase total PUFA. Intended omega-3 dose was 1. 8 g/d EPA, compared to nil, and both groups received "appropriate" dietary advice (not described further). This suggests increases in total PUFA (0.8% E n-3, 0.8% E PUFA), but increase in plasma PUFAs (sum of omega-3 and omega-6 fats, including EPA, DHA, DPA, ALA, LA, GLA, AA), was higher in control (+26.2 mg/mL) than intervention (+ 20 mg/mL). TC not reported, LDL change was equivalent (but all on statins). Difference in total PUFA appears < 10% of baseline PUFA intake assumed to be 6% E
Lorenz-Meyer 1996	Compared EPA + DHA vs omega-6, no intention to increase total PUFA. Intervention increased EPA + DHA 5.1 g/d vs 6 g/d LA, 0.9 g/d or 0.45% E difference, < 10% increase over assumed 6% E PUFA. No biomarker or TC or intake data reported
Mansel 1990	Did not aim to alter total PUFA, aimed to increase 0.48 g/d GLA or 4 kcal or 0.2 % E GLA , increase ~8.4 g/d LA or 76 kcal or 3.8 % E LA , total 4 % E n6 , estimated total PUFA dose 4 % E. No serum TC or tissue fatty acid levels reported, no dietary intake data. No deaths or cardiovascular events occurred, only breast cancer diagnoses reported
MAPT 2017	Compared EPA + DHA vs paraffin oil (non fat). Intervention 1.025 g/d DHA + EPA compared to flavoured paraffin oil. (Also aims 3 and 4 as above plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities). Intended increase 1.03 g/d EPA + DHA, 0.5% E n3, 0.5% E PUFA, < 10% more than assumed 6% E PUFA baseline

MARGARIN Bemelmans 2002	Omega-3 vs omega-6. Compared omega-3 (ALA-rich margarine, 80% fat of which 15% was ALA and 46% LA) with omega-6 (LA-rich margarine, 80% fat of which 0.3% was ALA and 58% LA) . Margarines eaten as desired, so doses unclear. Serum cholesterol ester fatty acid changes suggest rises in ALA in omega-3 arm and rises in LA in the LA arm, with rough equivalence in total PUFA between arms. TC fell slightly more in LA arms than ALA arms, but fell in all arms. Arms appear equivalent in total PUFA intake
MENU - Rock 2016	Compared walnut-rich moderate fat diet (ALA) vs moderate fat diet (MUFA), did not aim to increase total PUFA. Intervention was advice to follow walnut-rich higher fat diet (35% E fat with limited SFA, MUFA encouraged, including 42 g/d walnuts, 45% E CHO, 20% E protein) vs exactly as intervention goals without walnuts. Unclear how total PUFA altered in each arm, mean LDL at 1 year was 2.97 mmol/L in both arms, TC not reported. Red blood cell fatty acid ALA and LA reported at 1 year (summed 12.5% in intervention, 12.2% in control) but other fatty acids not reported. PUFA dose unclear, excluded
Michalsen 2006	Multifactorial - combination of diet (focusing on ALA and oily fish as well as Mediterranean diet more generally), exercise and stress-reduction programme and advice in intervention, general written dietary and stress advice in control
Middleton 2002	Intervention and control descriptions unclear. Compared EPA + DHA + GLA vs LA, but unclear which arm was higher in PUFA, or quantity of PUFA in either arm
Minnesota Coronary 1989	While participants were involved in this trial for over 1 year on average they could move in and out of the institution in which the trial took place, and therefore in and out of the trial over the duration of the trial. Most participants were not involved in the trial continuously for ≥ 1 year
Moy 2001	Aim was to reduce dietary fat (total and saturated fat reductions appear to have been achieved) but effects on PUFAs unclear (total PUFA, omega-6 and omega-3 intakes not reported)
NAT2 2015	No aim to increase total PUFA, aimed to increase omega-3 fats. Intervention was 1110 mg/d n-3 FAs (EPA: 270 mg/day DHA: 840 mg/day) vs olive oil capsules (containing 0.2 g total PUFA). Total PUFA dose would be 0.91 g/d, or 0.4% E PUFA. Red blood cell lipid EPA and DHA presented, but not total PUFA. Dietary intake data suggest 0.5% E difference in total PUFA between arms (< 10% increase from assumed 6% E from PUFA at baseline)
Norouzi 2014	Compared LCn3 with placebo (no details). Intervention 1.056 g/d LCn3 plus 0.056 g/d omega-6, 1.112 g/d PUFA in intervention, control group contents unclear, so unclear whether more PUFA vs less. No biomarker, TC or dietary intake data to help. No intention to increase total PUFA and no information on whether PUFA was increased substantially in one arm compared to the other, exclude
Norwegian - Natvig 1968	Aim was to increase vegetable oil intake, comparing ALA (linseed oil) with omega-6 (sunflower oil) . Intervention was linseed oil, 10 mL/d (55% ALA), 5.5 g/d ALA, 1.5g/d LA (7.04 g total PUFA) , control was sunflower oil, 10 mL/d (1.4% ALA), 0.14 g/d ALA, 6.3 g/d LA or 6.42 g/d omega-6 (6.56 g/d total PUFA). Intended total PUFA dose was 0.48 g/d lower total PUFA or 0.22% E from PUFA lower in intervention (< 10% change from assumed 6% E baseline). No biomarker or dietary intake data, except slightly lower TC at 6 months in intervention arm

(Continued)

NutriStroke 2009	Compared LCn3 with unclear placebo. No intention to increase total PUFA. Intervention 0.5 g/
Nutristroke 2009	d LCn3, assume 0.5 g/d PUFA. Control group contents unclear, but state no PUFA. PUFA dose 0.5 g/d or 0.23% E PUFA, < 10% increase from assumed 6% E PUFA baseline. No biomarker, TC or dietary intake data to confirm
OFAMI - Nilsen 2001	Omega-3 vs omega-6 comparison, aim to assess effects of omega-3 increase, total PUFA doses in each arm unclear, no dietary intake data provided
OMEGA 2014	Did not aim to alter total PUFA. Aimed to increase omega-3 fats, vs MUFA control, but only increased omega-3 fats by 0.4% E (< 10% of assumed baseline of 6% E from PUFA). No dietary intake data provided
OPAL - Dangour 2010	Aimed to increase omega-3 fats, not total PUFA, compared omega-3 supplement with olive oil, omega-3 dose $0.7~g/d$ or $0.3\%~E$ (< 10% of assumed baseline of 6% E from PUFA). No dietary intake data provided
ORIGIN 2012	Aimed to increase omega-3 fats, not total PUFA. Compared omega-3 supplement with olive oil placebo, EPA + DHA vs MUFA. Aimed to increase 0.84 g/d EPA + DHA, 0.4% E n-3, 0.4% E PUFA (< 10% of assumed baseline of 6% E from PUFA). No dietary intake data provided
Oslo Diet-Heart 1966	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
Oxford Retinopathy 1978	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
POUNDS Lost Sacks 2009	Manipulation of total fat intake, but no details of fat types aimed for or achieved in any arms
Ramirez-Ramirez 2013	Omega-3 vs omega-6 (DHA + EPA vs sunflower oil). Quantities of total PUFA in each arm unclear, but likely to have been similar (< 10% of assumed baseline of 6% E from PUFA). Aimed to assess omega-3 effects, no dietary intake data provided
Reed 2014	Omega-3 vs omega-6 (EPA + DHA vs GLA + sunflower oil). Doses of total PUFA in each arm unclear but likely to have been similar (< 10% of assumed baseline of 6% E from PUFA). Aimed to assess omega-3 effects and omega-6 effects, not total PUFA. Paper states that there were no differences between arms for TC or dietary intake
Risk and Prevention	Omega-3 vs MUFA, but small PUFA dose (intended to increase 0.86 g/d EPA + DHA, 0.4% E n3, 0.4% E PUFA). Aimed to assess effects of omega-3 fats, not total PUFA, intended dose too small (< 10% of assumed baseline of 6% E from PUFA). No difference between arms for change in TC from baseline to 5 years (P = 0.52)
Sandhu 2016	Aimed to increase omega-3 fats. Intended dose suggested higher omega-3 fats in Lovaza and Lovaza & Raloxifee compared to control and Raloxifene 30 mg (as no placebo was provided. However, plasma fatty acid concentration suggested that total PUFA was not higher in these arms. Mean summed plasma fatty acid omega-3 fats higher in Lovaza and Lovaza & Raloxifee arms compared to control and Raloxifene 30 mg at 2 years. However omega-6 fats were equivalently lower, mean total PUFA (summing omega-3 and omega-6) similar in both arms

Schirmer 2007	Compared n-6 (GLA) vs MUFA, did not aim to increase total PUFA. Intervention included 0.89 g/d GLA plus ~0.9 g/d LA or 0.8% E n6. control included 1 g/d LA, 0.45% E LA. Difference 0. 35% E omega-6, assume same for PUFA, < 10% more than assumed 6% E baseline total PUFA. No biomarker, TC or dietary intake data
SCIMO - von Schacky 1999	Aimed to increase omega-3 fats. Intended omega-3 dose was 1.03 g/d EPA + DHA, 0.5% E n-3. This would translate to 0.5% E PUFA, but the placebo was probably fairly rich in total PUFA. Excluded as probably < 10% increase in total PUFA in intervention compared to control. Erythrocyte phospholipid fatty acid composition confirmed rise in EPA and DHA but didn't report further PUFAs. Serum total cholesterol dropped very slightly more in intervention than control (TC -0.1mmol/L in int, -0.05mmol/L in cont from baseline to 24 months)
Shinto 2014	Compared EPA + DHA vs n-6, did not intend to increase total PUFA. Intervention 1.650 g/d LCn3, 1.65 g/d PUFA vs 3 g/d soybean oil (-60% PUFA), 1.8 g/d PUFA. Dose is 0.15 g/d PUFA, 0.07% E PUFA, < 10% change from assumed 6% E PUFA baseline. No biomarker (except red blood cell EPA + DHA), dietary intake or TC data
SHOT - Eritsland 1996	Aim was to increase omega-3 fats. Intervenion was omega-3 vs nil, and provided 3.3 g/d EPA + DHA, or 1.5% E from omega-3 fats. This suggests increase of 1.5% E from PUFA, but serum fatty acid PUFA assessments were 645 mg/L in the control (up 43 mg/L from 603 at baseline), and 621 mg/L (up 28 mg/L from 593) in the intervention group at 9 months, suggesting lower or equivalent total PUFA intake in the intervention compared with control. Serum TC remained constant over the trial in both arms
Sianni 2013	Control group contents unclear, so unclear if more PUFA vs less. Aimed to increase omega-3 fats, intervention group received 4 g/d omega-3 fats, placebo not described. As only an abstract could be found, and contact could not be established with the authors we excluded this trial
SMART Tapsell 2013	Compared fish + fish oil supplements vs fish + olive oil supplements vs olive oil supplements. Did not aim to increase total PUFA. Comparisons with olive oil supplement arm are multifactorial so excluded. Fish + fish oil supplements (capsules including 420 mg/d EPA + 210 mg/d DHA, 0.63 g/d EPA + DHA) vs fish plus olive oil supplements (1 g olive oil/d, assume 0.2 g/d PUFA) has equivalent diets with differing supplements between arms. Dose 0.43 g/d PUFA, 0.2% E from PUFA, < 10% increase from assumed 6% E PUFA at baseline
SOFA 2006	Aimed to increase omega-3 fats. Comparison was EPA + DHA (961 mg n-3 PUFAS) vs MUFA + omega-6 (2 g/d high-oleic acid sunflower oil). Omega-3 dose was only 0.96 g/d, or 0.4% E from omega-3. As there was some PUFA in the placebo it was unlikely that total PUFA was increased more than 10% of baseline. No biomarker data found to confirm or refute this
Sofi 2010	Aimed to increase omega-3 fats. Comparison was EPA + DHA (6.5 mL/d olive oil enriched with n-3 plus dietary recommendations, 0.83 g n-3/d of which 0.47 g/d EPA & 0.24 g/d DHA) vs MUFA (6.5 mL/d olive oil plus dietary recommendations). Omega-3 dose was 0.71 g/d EPA + DHA, 0.3% E n-3, equivalent to 0.3% E PUFA (< 10% increase from assumed 6% E PUFA baseline). No fatty acid biomarker data, TC fell more in control than intervention
STARS 1992	Intervention encouraged to increase plant-derived soluble fibre as well as alter dietary fats, multi-factorial

Stoll 2001	Ongoing trial. NCT00010868. The PI, Andrew Stoll, appears to have been struck off the medical register in Massachusetts in 2011 (Commonwealth of Massachusetts Board of Registration in Medicine, Adjudicatory Case number 2011-026) so it has not been possible to contact him and no publication of results has been found
STRENGTH	Ongoing trial. Intervention omega-3 carboxylic acid capsule (Epanova, not less than 800 mg/g) and statin vs corn oil placebo capsule and statin. Omega-3 vs omega-6, unlikely to reach PUFA dose of > 1.33 g/d or 0.6% E
SU.FOL.OM3 Galan 2010	Compared EPA + DHA vs non-fat placebo, no intention to increase total PUFA. Intervention 400 mg/d EPA and 200 mg/d DHA compared to liquid paraffin with fish flavour. Intended dose 0.6 g/d EPA + DHA, 0.3% E PUFA, < 10% change from assumed 6% E PUFA baseline. No biomarker (aside from plasma EPA + DHA), TC (apart from baseline) or dietary intake data provided
Søndergaard 2003	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
Tande 2016	Compared EPA + DHA vs MUFA, did not intend to increase total PUFA. Intervention 2 g/d calanus oil (85% wax ester with a sum of neutral lipids > 90%, 11% oil is EPA + DHA, or 0.22 g/d EPA + DHA), control 2 g/d olive oil (analysis indicated this olive oil was primarily oleic acid (76.9%), palmitic acid (10.2%), and linoleic acid (7.7%), assumed 0.14 g/d LA), overall dose 0. 08 g/d PUFA, 0.04% PUFA. < 10% increase from assumed 6% E PUFA. TC increased by 0.02 mmoL/L in intervention to 1 year, fell 0.08 mmoL/L in control, no further biomarker or intake data
Tay 2015	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
THIS DIET - Tuttle 2008	Aim was to achieve a Mediterranean-style diet, and compare it to a low-fat diet. All intervention and control participants were advised to reduce SFA and dietary cholesterol, increase fruits and vegetables and whole grains. In addition intervention participants were encouraged to increase coldwater fish and oils from olives, canola and soybeans. Plasma fatty acid composition suggested that omega-3 increased in the intervention arm compared to control (rising 0.1% in control, rising 0.6% in intervention) while omega-6 fats reduced in the intervention (rising 0.7% in control, falling 0.1% in intervention). This confirms dietary intake data suggesting that total PUFA increased by 0.9% E in control, and increased by only 0.1% E in intervention, to equivalence at 24 months (total PUFA intake at 24 months 5.7% E, SD 3.1 in control, 5.7% E, SD 2.4 in intervention). No total PUFA difference between arms during trial, so excluded
VITAL	Ongoing trial. Intervention omega-3 (Omacor fish oil, EPA + DHA 1 g/d: 465 mg EPA; 375 mg DHA) vs placebo (plus or minus vitamin D3). Placebo unclear but very unlikely to attain a dose of > 1.33 g/d PUFA or 0.6% E
Weinstock-Guttman 2005	Aim was to compare low fat diet (15% E from fat) plus EPA + DHA supplements (3.3 g/d EPA + DHA, 1.5% E n3) with low-fat diet (30% E from fat) plus olive oil capsules. Total PUFA in each arm (aimed or achieved) is not clear. Serum fatty acids were assessed, data reported on MUFA, EPA, DHA, DPA, combined omega-3 fats and SFA, but not total fat intake or total PUFAs. TC was not reported and LDL rose slightly in both groups, more in the control (30% E fat) than

(Continued)

	intervention (15% E fat). Dietary intake not reported
WHI 2006	Dietary intervention was of dietary fat and also fruit and vegetables, multifactorial
Zhang 2016	Compared DHA vs corn oil (n6). No aim to increase total PUFA, intervention 1.0 g/d DHA, 0.45% E n3, control 1.1 g/d PUFA, 0.5% E PUFA, dose 0.05% E PUFA, < 10% increase from assumed 6% E PUFA baseline. No fatty acid (except very small increase in serum DHA in intervention, unclear if statistically significant), TC or dietary intake data
Özaydin 2011	Compared omega-3 supplement with nil (no placebo). Intended omega-3 dose was increase 0.6 g/d EPA + DHA, 0.3% E n-3, 0.3% E PUFA. Baseline total PUFA not reported, nor intake or body marker data. Assume baseline 6% E PUFA, dose < 10% increase

AA: arachidonic acid; ALA: alpha-linolenic acid (a plant-based omega-3 fat); CHO: carbohydrate; DHA: docosahexaenoic acid (a fish-based omega-3 polyunsaturated fat); DPA: docosapentaenoic acid (a fish-based omega-3 polyunsaturated fat); EPA: eicosapentaenoic acid (a fish-based omega-3 polyunsaturated fat); LA: linoleic acid (an omega-6 polyunsaturated fat); LDL: low density lipoprotein (a fraction of TC, measured in human blood); MUFA: monounsaturated fatty acid or monounsaturated fat; PUFA: polyunsaturated fatty acid or polyunsaturated fat; SFA: saturated fatty acid or saturated fat; TC: total cholesterol (measured in human blood)

Characteristics of ongoing studies [ordered by study ID]

AC Omega3

Trial name or title	The Aboriginal cardiovascular omega-3 randomised controlled trial (AC Omega3)
Methods	RCT
Participants	Indigenous Australian adults with stable coronary artery disease
Interventions	Each for 12 months: Arm 1: omega-3 (1800 mg/d AlaskOmega: 3 capsules/d: 400 mg EPA and 200 mg DHA) Arm 2: placebo mixed oil capsules (1000 mg/d: 3 capsules/d containing palm oil, gelatin, glycerol, sunflower oil, rapeseed oil, mixed tocopherols, and a "small amount" of fish oil ((or taste) to aid blinding)
Outcomes	Primary: serum non-HDL cholesterol Secondary: triglycerides, total cholesterol, LDL, HDL, lipid functionality by cholesterol efflux and CETP, heart rate variability, platelet function and thrombosis markers, inflammation markers, cumulative combined rate of major adverse cardiac events (including death, non-fatal MI, unstable angina, non-fatal stroke, revascularisation and cardiac-related hospital admissions)
Starting date	Registered on Trials Registry: 10 July 2014 Trial start date: 1 October 2014 Trial completion date est: unclear

AC Omega3 (Continued)

Contact information	Alex Brown (PI), Wardliparingga Aboriginal Unit, Adelaide, Australia, alex.brown@sahmri.com
Notes	ACTRN12614000732684 Alex Brown contacted in 2016: confirmed trial is actively recruiting

ACTRN12610000594022

Trial name or title	Clinical efficacy of fish oil as adjunct therapy for patients with chronic periodontitis
Methods	RCT
Participants	Adults (25-80 years, non-smokers) with newly diagnosed severe but non aggressive periodontitis
Interventions	Each for 13 months: Arm 1: fish oil rich in EPA (6 x 500 mg capsules/d: 277 mg EPA; 27 mg DHA) and standard periodontal treatment (scaling and debridement) Arm 2: fish oil rich in DHA (6 x 500 mg capsules/d: 66 mg EPA; 258 mg DHA) and standard periodontal treatment Arm 3: soya oil placebo (6 x 500 mg capsules/d) and standard periodontal treatment
Outcomes	Primary: probing pocket depth, clinical attachment level (CAL) Secondary: inflammatory biomarkers in gingival crevicular fluid, erythrocyte omega-3, C-reactive protein
Starting date	Registered on Trials Registry: 23 July 2010 Trial start date: July 2010 Trial completion date est: unclear
Contact information	Mark Bartold, University of Adelaide, mark.bartold@adelaide.edu.au
Notes	ACTRN12610000594022 PhD, Boram Park, available giving 4-month outcome data for pilot trial n = 33 participants Mark Bartold written to in 2016. Confirmed preparing full publications for submission

ACTRN12613000034730

Trial name or title	Intervention of testosterone & fish oil for the prevention of Alzheimer's disease: InTrePad
Methods	RCT
Participants	PiB-PET (Pittsburgh compound B)-positive men aged ≥ 60 years with subjective memory complaints
Interventions	Each for 56 weeks: Arm 1: DHA capsules (1720 mg/d) and testosterone undecanoate (intramuscular injection 1000 mg/4 mL every 8 weeks) Arm 2: placebo DHA and testosterone undecanoate (intramuscular injection 1000 mg/4 mL every 8 weeks) Arm 3: placebo DHA and placebo testosterone

ACTRN12613000034730 (Continued)

Outcomes	Primary: PiB score Secondary: neuropsychological, mood and daily functioning questionnaires, beta amyloid levels, fluo-rodeoxyglucose to assess brain glucose metabolism, inflammatory and oxidative biomarkers, hippocampal volume, quality of life, safety and tolerability of treatment
Starting date	Registered on Trials Registry: 14 January 2013 Trial start date: 28 February 2013 Trial completion date est:
Contact information	Ralph Martins (PI), Sir James McCusker Alzheimer's Disease Research Unit, Hollywood Medical Centre, Nedlands, Australia, r.martins@ecu.edu.au
Notes	ACTRN12613000034730 Ralph Martins written to in 2016- no response

AFORRD

Trial name or title	Atorvastatin in factorial with omega-3 fatty acid risk reduction in diabetes (AFORRD)
Methods	RCT
Participants	People with type 2 diabetes with no known CVD and not taking lipid-lowering therapy, adults (> 18 years) N: intervention 397, control 403 (analysed intervention 371, control 361)
Interventions	Each for 12 months: Arm 1: atorvastatin (Lipitor 20 mg/d) and olive oil placebo (2 g/d) Arm 2: omega-3 (Omacor 2 g/d: 46% EPA, 38% DHA) and placebo tablets for atorvastatin Arm 3: atorvastatin (Lipitor 20 mg/d) and Omega-3 (Omacor 2 g/d: 46% EPA, 38% DHA) Arm 4: placebo tablets for atorvastatin and olive oil placebo (2 g/d)
Outcomes	Primary: lipid profiles Secondary: phytosterol changes, HbA_{1c} , estimated CVD risk using the UK Prospective Diabetes Study risk engine
Starting date	Registered on Trials Registry: 4 April 2004 Trial start date: 1 November 2004 Trial completion date est: 31 July 2006
Contact information	Rury Holman, Oxford Centre for Diabetes
Notes	ISRCTN76737502 Rury Holman contacted in 2016: confirmed results are not yet published, but planned

Beyond Aging Project

Trial name or title	The Beyond Ageing Project phase 2: a selective prevention trial using novel pharmacotherapies in an older age cohort at risk for depression
Methods	RCT
Participants	Older adults (≥ 60 years) at risk of depression (K-10 score ranging from 16-29) who initially participated in the first Beyond Ageing Project
Interventions	Each for 12 months: Arm 1: omega-3 (4 capsules, total 2 g/d: 1200 mg EPA and 800 mg DHA) and placebo microcrystalline cellulose (1 capsule) Arm 2: paraffin oil placebo (4 capsules) and sertraline hydrochloride (1 capsule, 50 mg) Arm 3: paraffin oil placebo (4 capsules) and placebo microcrystalline cellulose (1 capsule)
Outcomes	Primary: depressive symptoms (PHQ-9) Secondary: cognitive decline, Mini Mental State Exam, brain metabolism, hippocampal volume, anxiety (Generalized Anxiety Disorder-7 (GAD-7)), disability (World Health Organziation Disability Assessment Schedule-II (WHODAS-II)), sleeping problems (Pittsburgh Sleep Quality Index (PSQI)), exercise (Active Australian Survey)
Starting date	Registered on Trials Registry: 12 January 2010 Trial start date: June 2011 Trial completion date est: Main results expected in 2017
Contact information	Ian Hickie (PI), Brain and Mind Centre, University of Sydney, ian.hickie@sydney.adu.au
Notes	ACTRN12610000032055

Chandrakala 2010

Trial name or title	Long-term effects of a reduced fat diet intervention in pre-diabetes
Methods	RCT
Participants	Participants with pre-diabetes (IFG/IGT), 201 participants discussed in 1 abstract, 134 in a later abstract
Interventions	Each for 3 years: Arm 1: reduced-fat diet (fat content ≤ 20% total energy, ratio of PUFA/SFA 0.8 to 1.0) Arm 2: normal/control diet
Outcomes	Incidence of diabetes, BMI, lipids, insulin, plasma glucose, HbA1c, BP, nutritional intake
Starting date	Registered on Trials Registry: no registration found Trial start date: not stated Trial completion date est: not stated
Contact information	Chandrakala Galla, chandrakala.galla@gmail.com; Arpana Gaddam, dr.arpanag@gmail.com

Chandrakala 2010 (Continued)

Notes	We wrote to trial authors in 2016: Dr Gaddam confirmed work submitted as a PhD but not published in full. Requested copy of PhD thesis, but no reply to date Funding: DiabetOmics India
	runding: DiabetOmics India

n-3 for Vascular Cognitive Aging

Trial name or title	n-3 PUFA for vascular cognitive aging
Methods	RCT
Participants	Older adults (≥ 80 years) at high risk for cognitive decline and dementia of Alzheimer's type
Interventions	Each for 3 years: Arm 1: omega-3 fish oil (1.65 g/d EPA + DHA) Arm 2: soybean oil placebo (1.65 g/d)
Outcomes	Primary: total cerebral white matter volume Secondary: biomarkers of endothelial health, total brain atrophy, medial temporal lobe atrophy, ventricular expansion, Trail Making Test part B, digit symbol Wechsler Adult Intelligence Scale-Revised (WAIS-R), cerebral blood flow, fractional anisotropy within frontal gyri
Starting date	Registered on Trials Registry: 24 September 2013 Trial start date: May 2014 Trial completion date est: March 2019
Contact information	Alena Borgatti, borgatti@ohsu.edu; James Dursch, dursch@ohsu.edu; Gene Bowman and Lynne Shinto (PIs), Oregon Health and Science University
Notes	NCT01953705

n-3 on plasma lipid

Trial name or title	Influence of different sources of n-3 fatty acid on plasma lipid in moderately hypercholesterolaemic subjects
Methods	RCT
Participants	Adults (40-65 years) with mild to moderate hypercholesterolaemia
Interventions	Arm 1: EPA/DHA 1.8 g/d Arm 2: EPA/DHA 3.6 g/d Arm 3: ALA 4 g/d Arm 4: placebo
Outcomes	Fatty acids, lipids, cytokines (IL-6, IL-1a)

n-3 on plasma lipid (Continued)

Starting date	Registered on Trials Registry: 13 March 2012 Trial start date: unclear Trial completion date est: unclear
Contact information	Su Yixiang, Sun-Yat Sen University, China, suyx@mail.sysu.edu.cn; Zhou Quan, Guangzhou Medical University, joan_zq@126.com
Notes	ChiCTR-TRC-12002014 Su Yixiang and Zhou Quan contacted in 2016: no response

NCT00309439

Trial name or title	Studies of serum PSA to help resolve the current implication of alpha-linolenic acid and prostate cancer
Methods	RCT
Participants	Adults 18-77 years
Interventions	Arm 1: ALA-rich diet Arm 2: control (not detailed)
Outcomes	PSA, atrial fibrillation
Starting date	Registered on Trials Registry: 29 March 2006 Trial start date: unclear Trial completion date est: unclear
Contact information	David Jenkins, University of Toronto, nutritionproject@smh.toronto.on.ca
Notes	NCT00309439 David Jenkins written to in 2016: confirmed not published in full and data incomplete

Trial name or title	Arrhythmia prevention with an alpha-linolenic enriched diet
Methods	RCT, parallel, 2 arms, 12 months
Participants	98 people with successful atrial fibrillation electrical cardioversion
Interventions	Canola margarine and oil, rich in ALA, versus a conventional diet (control), for 1 year
Outcomes	Length of time to first recurrence of atrial fibrillation
Starting date	June 1999, expected finish date June 2003, registered December 2006 so appears to have been carried out

NCT00410020 (Continued)

Contact information	Principal Investigator: Jean-Paul Broustet, MD, PhD, Universitary Hospital Haut-Lévêque Bordeaux France
Notes	NCT00410020, registered Dec 2006, no publication found

NCT01047449

Trial name or title	Improving the results of heart bypass surgery using new approaches to surgery and medication (SUPERI-ORSVG)
Methods	RCT
Participants	Adults having coronary artery bypass graft (CABG) using saphenous vein graft (SVG)
Interventions	Each for 12 months: Arm 1: fish oil supplements (2 x 1 g/d Ocean Nutrition capsules: 55% fish oils EPA:DHA 33%:22%) and SVG conventionally harvested Arm 2: placebo and SVG conventionally harvested Arm 3: fish oil supplements (2 x 1 g/d Ocean Nutrition capsules: 55% fish oils EPA:DHA 33%:22%) and SVG no-touch harvest Arm 4: placebo and SVG no-touch harvest
Outcomes	Primary: proportion of grafts occluded Secondary: significant stenosis, adverse SVG harvesting events, composite outcome of all-cause mortality, non-fatal MI and repeat revascularisation
Starting date	Registered on Trials Registry: 12 Jan 2010 Trial start date: July 2011 Trial completion date est: Dec 2016
Contact information	Stephen Fremes, Sunnybrook Health Sciences Centre (PI)
Notes	NCT01047449

Trial name or title	Long-term effects of interventional strategies to prevent cognitive decline in elderly (MAPT PLUS)
Methods	RCT - extension of MAPT trial
Participants	Participants of MAPT trial
Interventions	Follow-up, 2-year extension of participants in MAPT, after completion of MAPT interventions
Outcomes	Primary: cognitive and functional status (Grober and Buschke test) Secondary: markers of cerebral atrophy, cost effectiveness

NCT01513252 (Continued)

Starting date	Registered on Trials Registry: 30 December 2011 Trial start date: December 2011 Trial completion date est: November 2016
Contact information	Bruno Vellas (PI), University Hospital, Toulouse, vellas.b@chu-toulouse.fr
Notes	NCT01513252 Bruno Vellas written to in 2016- no response

NCT01784042

Trial name or title	Dietary energy restriction and omega-3 fatty acids on mammary tissue
Methods	RCT
Participants	Overweight women (30-55 years) with increased breast cancer risk
Interventions	For 1 year: Arm 1: Lovaza (omega-3-acid ethyl esters) Arm 2: Lovaza and dietary energy restriction Arm 3: placebo Arm 4: placebo and dietary energy restriction
Outcomes	Ki67 expression at 1 year
Starting date	Registered on Trials Registry: 31 January 2013 Trial start date: March 2013 Trial completion date est: March 2018
Contact information	Andrea Manni, Hershey Medical Centre, amanni@hmc.psu.edu (PI) or Cynthia DuBrock, cdubrock@hmc.psu.edu
Notes	NCT01784042

Trial name or title	Dry eye assessment and management trial (DREAM)
Methods	RCT
Participants	Adults with dry eye
Interventions	Each for 2 years Arm 1: omega-3 supplements (2000 mg EPA + 1000 mg DHA/d as 5 gelcaps) Arm 2: olive oil supplements (5 gelcaps)

NCT02128763 (Continued)

Outcomes	Primary: Ocular Surface Disease Index (OSDI) score Secondary: other eye health measures, SF-36, healthcare utilisation costs, cost effectiveness
Starting date	Registered on Trials Registry 28 April 2014 Trial start date: November 2014 Trial completion date est: July 2017
Contact information	Penny Asbell, Mount Sinai Icahn School of Medicine (Trial Chair), Maureen Maguire, University of Pennsylvania (PI)
Notes	NCT02128763

NCT02211560

Trial name or title	Investigating a phosphatidylserine based dietary approach for the management of mild cognitive impairment
Methods	RCT
Participants	People with mild cognitive impairment (MCI) aged 65-85 years
Interventions	Each for 24 months: Arm 1: phosphatidylserine omega-3 (DHA enriched) Arm 2: placebo cellulose capsules
Outcomes	Primary: selective reminding test (SRT) Secondary: MMSE, neurological battery test (NBT), dementia (DSM-4 criteria), mini sleep questionnaire (MSQ), Hamilton Anxiety rating scale (HAM-A), safety and adverse events
Starting date	Registered on Trials Registry: 6 August 2014 Trial start date: September 2014 Trial completion date est: September 2019
Contact information	Nadia Niemerzyanski, nadiaN@enzymotec.com; Yael Richter, yaelr@enzymotec.com
Notes	NCT02211560

Trial name or title	Omega-3 fatty acids and ERPR(-)HER2(+/-) breast cancer prevention
Methods	RCT
Participants	Women at risk for recurrent breast cancer- with prior diagnosis of stage 0-III breast cancer and completion of surgery, chemotherapy or trastuzumab or radiation therapy

NCT02295059 (Continued)

Interventions	Each for 12 months: Arm 1: omega-3 high-dose capsules (5 g/d EPA + DHA) Arm 2: omega-3 low-dose capsules (0.9 g/d EPA + DHA)
Outcomes	Primary: breast adipose tissue metabolites Secondary: cytomorphology or cell proliferation of mammary epithelial cells, DNA promoter methylation and pro-inflammatory gene expression in mammary epithelial and adipose tissue
Starting date	Registered on Trials Registry: 14 October 2014 Trial start date: August 2014 Trial completion date est: January 2019
Contact information	Anitra Sumbry, anitra.sumbry@osumc.edu; Lisa Yee (PI), Ohio State University
Notes	NCT02295059

Trial name or title	Enabling reduction of low-grade inflammation in seniors (ENRGISE)
Methods	RCT
Participants	People aged 70+ years with self-reported walking or stair-climbing difficulty
Interventions	Each for 1 year Arm 1: omega-3 fish oil (1.4 g/d for 6 months, possibly increasing to 2.8 g/d) Arm 2: losartan 25 mg/d Arm 3: placebo corn oil (for omega-3) plus placebo cellulose (for losartan) Arm 4: omega-3 plus losartan Arm 5: placebo corn oil (for omega-3) Arm 6: placebo cellulose (for losartan)
Outcomes	Primary: IL6, 400-meter walk test Secondary: short physical performance battery, frailty, hand grip strength, knee dynamometry, Short Form (SF)-36
Starting date	Registered on Trials Registry 3 February 2016 Trial start date: February 2016 Trial completion date est: March 2018
Contact information	Jane Lu janelu@ufl.edu Michael Stancil mstancil@ufl.edu
Notes	NCT02676466

NCT02719327

Trial name or title	Impact of icosapent ethyl on Alzheimer's disease (AD) biomarkers in preclinical adults
Methods	RCT
Participants	Cognitively healthy adults aged 50-70 years whose parents had AD
Interventions	Each for 18 months: Arm 1: icosapent ethyl EPA (Vascepa) 4 g/d gel cap Arm 2: matching gel cap placebo
Outcomes	Primary: cerebral blood flow by magnetic resonance imaging Secondary: cerebrospinal fluid biomarkers of Alzheimer's disease, cognitive performance (preclinical Alzheimer's cognitive composite, PACC)
Starting date	Registered on Trials Registry: 21 March 2016 Trial start date: December 2016 Trial completion date est: November 2021
Contact information	Cynthia Carlsson, cynthia.carlsson@va.gov; Elena Beckman, elena.beckman@va.gov
Notes	NCT02719327

OMEMI

Trial name or title	Omega-3 fatty acids in elderly patients with myocardial infarction trial (OMEMI)
Methods	RCT
Participants	Elderly patients (70-82 years) with acute MI
Interventions	Each for 24 months: Arm 1: omega-3 capsules, 3/d (Pikasol, total of 1.8 g/d EPA + DHA) and standard therapy Arm 2: corn oil placebo, 3/d and standard therapy
Outcomes	Primary: composite of total mortality, first non-fatal recurring acute MI, stroke and revascularisation Secondary: new onset atrial fibrillation, adipose tissue, serum fatty acids, makers of endothelial function, inflammation, coagulation and fibrinolytic activity, genes associated with atherothrombosis
Starting date	Registered on Trials Registry: 16 April 2013 Trial start date: November 2012 Trial completion date est: November 2019
Contact information	Svein Solheim, Center for Clinical Heart Research, Oslo University Hospital, arnljot.tveit@vestreviken.no
Notes	NCT01841944

REDUCE-IT

Trial name or title	Reduction of cardiovascular events with EPA-intervention trial (REDUCE-IT)
Methods	RCT
Participants	Patients (45 years or over) with hypertriglyceridaemia, with cardiovascular disease or at high risk for cardiovascular disease, and on statin
Interventions	Each for 4-6 years: Arm 1: EPA ethyl ester (AMR101 4 g/d) Arm 2: placebo
Outcomes	Primary: composite of CV death, MI, stroke, coronary revascularisation and hospitalisation for unstable angina Secondary: incidence of additional cardiovascular events, lipid and lipoprotein levels
Starting date	Registered on Trials Registry: 13 December 2011 Trial start date: November 2011 Trial completion date est: December 2017
Contact information	Deepak Bhatt (PI), Brigham and Women's Hospital
Notes	NCT01492361

seAFOOD

Trial name or title	The seafood (systematic evaluation of aspirin and fish oil) polyp prevention trial
Methods	RCT
Participants	NHS Bowel Cancer Screening Programme patients (55-73 years) identified as "high risk" (\geq 5 small adenomas; or \geq 3 adenomas with at least one being \geq 10 mm in diameter) after their 1st screening colonoscopy
Interventions	Each for 12 months: Arm 1: EPA (ALFA capsules: 2 x 500 mg/d = 2 g/d) and aspirin placebo (1/d) Arm 2: EPA placebo (capric and caprylic acid triglycerides: 2/d) and aspirin EC (1/d = 300 mg/d) Arm 3: EPA (ALFA capsules: 2 x 500 mg/d = 2 g/d) and aspirin EC (1/d = 300 mg/d) Arm 4: EPA placebo (capric and caprylic acid triglycerides: 2/d) and aspirin placebo (1/d)
Outcomes	Primary: number of participants with ≥ 1 adenomas at 12 months Secondary: adverse events, number of "advanced" adenomas per participant, number of "high risk" participants re-classified as "intermediate risk", number participants with ≥ 1 advanced adenomas, adenoma region in the colorectum, total number of adenomas per participant, number of participants with colorectal cancer, levels of bioactive lipid mediators e.g. omega-3
Starting date	Trial Registration entry: 6 May 2011 Trial start date: 30 May 2011 Estimated trial completion: 31 July 2017

seAFOOD (Continued)

Contact information	Mark Hull, Leeds Institute of Molecular Medicine, m.a.hull@leeds.ac.uk
Notes	ISRCTN05926847 EudraCT 2010-020943-10 www.seafood-trial.co.uk

UMIN000012825

Trial name or title	Effect of PUFA on vascular healing process in hypercholesterolemic patients with ACS
Methods	RCT
Participants	Hypercholesterolemic patients (20-80 years) with acute coronary syndrome who have received successful optical coherence tomography (OCT)-guided percutaneous coronary intervention (PCI)
Interventions	Each for 12 months: Arm 1: intensive lipid-lowering therapy with both statin and EPA + DHA Arm 2: intensive lipid-lowering therapy with both statin and EPA Arm 3: standard lipid-lowering therapy with statins
Outcomes	Primary: changes in OCT parameter Secondary: lipids, serum plasma profile, inflammatory parameters, adverse cardiovascular events
Starting date	Registered on Trials Registry: 1 February 2014 Trial start date: 1 February 2014 Trial completion date est: 30 June 2019
Contact information	Shiro Uemura (PI), Nara Medical University, Japan, suemura@naramed-u.ac.jp
Notes	UMIN000012825

BMI: Body Mass Index; CETP: cholesteryl ester transfer protein; CVD: cardiovascular disease; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; HDL: high density lipoprotein: LDL: low density lipoprotein: MI: myocardial infarction; MMSE: Mini Mental State Examination; PSA: prostate-specific antigen; RCT: randomised controlled trial;

DATA AND ANALYSES

Comparison 1. Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ALL-CAUSE MORTALITY	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
2 All-cause mortality - SA	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Low risk of bias for	11	9639	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.87, 1.22]
allocation concealment				
2.2 Low risk of bias for attention	17	13622	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.07]
2.3 Low risk of bias for compliance	10	4776	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
2.4 Low summary risk of bias	5	8092	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.26]
2.5 Trials registry or pre-2010	22	18852	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.08]
2.6 No industry funding	9	4508	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.84, 1.42]
2.7 Randomised 100+ participants	20	19029	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.08]
2.8 Randomised 250+ participants	11	17457	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.10]
3 All-cause mortality - SA fixed-effect	24	19290	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.07]
4 All-cause mortality - subgroup by PUFA dose	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
4.1 total PUFA < 1.0% E	5	1054	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.34]
4.2 total PUFA 1.0 to < 2.0% E	9	13766	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.13]
4.3 total PUFA 2.0 to < 5.0% E	4	2295	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.20]
$4.4 \text{ total PUFA} \ge 5.0\% \text{ E}$	6	2175	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.86, 1.26]
5 All-cause mortality - subgroup by duration	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
5.1 Medium duration 1 to < 2 years	8	1940	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.48, 1.55]
5.2 Medium-long duration 2 to < 4 years	11	8219	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.82, 1.10]
5.3 Long duration 4+ years	5	9131	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
6 All-cause mortality - subgroup by primary or secondary prevention	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
6.1 Primary prevention of CVD	13	9549	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.20]
6.2 Secondary prevention of CVD	11	9741	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]
7 All-cause mortality - subgroup by baseline PUFA dose	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]

7.1 Baseline total PUFA < 6% E	4	3643	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.14]
7.2 Baseline total PUFA 6 to < 11% E	5	7826	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]
7.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Baseline total PUFA unclear	15	7821	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
8 All-cause mortality - subgroup by replacement	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 PUFA replaced SFA	6	4154	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.15]
8.2 PUFA replaced	11	12526	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.12]
monounsaturated fats				
8.3 PUFA replaced carbohydrate	5	2965	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.58, 1.70]
8.4 PUFA replaced protein	2	529	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.44]
8.5 PUFA replaced unclear	6	1227	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.39, 1.14]
9 All-cause mortality - subgroup by sex	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
9.1 > 70% men	13	10252	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]
9.2 > 70% women	1	2437	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.43, 1.65]
9.3 men & women	8	6498	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.29]
9.4 sex not reported	2	103	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.51, 1.59]
10 All-cause mortality - subgroup by age	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
10.1 Mean age < 50 years	6	1852	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.95, 2.27]
10.2 Mean age 50 to < 65 years	12	6040	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
10.3 Mean age 65+ years	6	11398	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
11 All-cause mortality - subgroup by statin use	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
11.1 < 50% on statins	18	13399	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.10]
11.2 50+% on statins	4	5353	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.26, 1.51]
11.3 Percentage on statins unclear	2	538	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.56, 2.37]
12 All-cause mortality - subgroup by intervention type	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
12.1 Dietary advice	4	4739	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.23]
12.2 Supplemental foods & diet provided	5	11104	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]
12.3 Supplements (capsules & unusual foods)	12	2391	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.52, 1.11]
12.4 Any combination	3	1056	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.72, 1.74]
13 CORONARY HEART DISEASE (CHD) EVENTS: myocardial infarction (fatal or non-fatal) or angina	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
14 CHD events - SA	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Low risk of bias for	5	5946	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.73, 1.78]
allocation concealment			· · · · · · · · · · · · · · · · · · ·	2

14.2 Low risk of bias for attention	11	7090	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.02]
14.3 Low risk of bias for compliance	7	4006	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.65, 1.17]
14.4 Low summary risk of bias	4	5826	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.76, 1.81]
14.5 Trials registry or pre- 2010	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
14.6 No industry funding	4	1073	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.63]
14.7 Randomised 100+ participants	12	9869	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.08]
14.8 Randomised 250+ participants	6	8958	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
15 CHD events - SA fixed-effect	15	10076	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.82, 0.99]
16 CHD events - subgroup by PUFA dose	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
16.1 total PUFA < 1.0% E	3	829	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.20, 4.89]
16.2 total PUFA 1.0 to < 2. 0% E	4	5170	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.66, 1.13]
16.3 total PUFA 2.0 to < 5. 0% E	3	2224	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.04]
16.4 total PUFA > 5.0% E	5	1853	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.54, 1.36]
17 CHD events - subgroup by duration	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
17.1 Medium duration 1 to < 2 years	6	1073	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.30]
17.2 Medium-long duration 2 to < 4 years	5	7204	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
17.3 Long duration 4+ years	4	1799	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.46, 1.35]
18 CHD events - subgroup by primary or secondary prevention	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
18.1 Primary prevention of CVD	6	1710	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.25, 1.11]
18.2 Secondary prevention of CVD	9	8366	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.09]
19 CHD events - subgroup by baseline PUFA dose	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
19.1 Baseline total PUFA < 6% E	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
19.2 Baseline total PUFA 6 to < 11% E	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.68, 2.01]
19.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.4 Baseline total PUFA unclear	12	6739	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.06]
20 CHD events - subgroup by replacement	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 PUFA replaced saturated fats	4	3730	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.19]

20.2 PUFA replaced	9	7079	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.20]
monounsaturated fats				
20.3 PUFA replaced	2	156	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.12, 2.65]
carbohydrate				
20.4 PUFA replaced protein	1	393	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.69, 1.37]
20.5 PUFA replaced unclear	3	469	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.09, 3.52]
21 CHD events - subgroup by sex	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
21.1 > 70% men	10	9269	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
21.2 > 70% women	1	140	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.08, 44.38]
21.3 men & women	2	222	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.13, 0.51]
21.4 sex not reported	2	445	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.66, 2.50]
22 CHD events - subgroup by age	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
22.1 Mean age < 50 years	1	458	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.00, 2.67]
22.2 Mean age 50 to < 65	9	3204	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.03]
years				
22.3 Mean age 65+ years	3	5921	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.04]
22.4 Mean age unclear	2	493	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.06, 4.64]
23 CHD events - subgroup by	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
statin use				
23.1 < 50% on statins	13	5001	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.66, 1.09]
23.2 50+% on statins	2	5075	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.17]
24 CHD events - subgroup by	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
intervention type				
24.1 Dietary advice	2	2135	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.15, 1.77]
24.2 Supplemental foods & diet provided	2	5683	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.04]
24.3 Supplements (capsules & unusual foods)	9	1407	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.56, 1.37]
24.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.74, 2.02]
25 STROKE - fatal & non fatal	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
26 Stroke - SA	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 Low risk of bias for	4	6022	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.55, 2.38]
allocation concealment			, , ,	
26.2 Low risk of bias for	8	11858	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.51, 0.98]
attention			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	, [, .,,]
26.3 Low risk of bias for	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
compliance			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
26.4 Low summary risk of	3	5686	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.49, 2.23]
bias		,,,,,		
26.5 Trials registry or pre-	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
2010		11, 12	14011 14110 (11111, 14114011, 7577 61)	0.71 [0.70, 1.11]
26.6 No industry funding	2	851	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.32, 8.62]
26.7 Randomised 100+	10	14662	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.56, 1.45]
participants				.,, . [.,, ., .,.,]
26.8 Randomised 250+	8	14291	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.60, 1.60]
participants	3	1 12/1	1001 1 mile (111 11, 1 mille) (11, 7) (1)	0.70 [0.00, 1.00]
27 Stroke - SA fixed-effect	11	14742	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.11]
28 Stroke - subgroup by PUFA	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
dose		1 1/ 12	1001 1 mile (111 11, 1 mille) (11, 17, 10 of)	0.71 [0.70, 1.11]
28.1 total PUFA < 1.0% E	4	1098	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.14, 6.55]
	-		(,, , , , , , , , , , , , ,	[, 4.22]

28.2 total PUFA 1.0 to < 2. 0% E	2	9834	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.07]
28.3 total PUFA 2.0 to < 5. 0% E	2	2113	Risk Ratio (M-H, Random, 95% CI)	3.25 [0.99, 10.72]
28.4 total PUFA > 5.0% E	3	1697	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.33]
29 Stroke - subgroup by duration	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
29.1 Medium duration 1 to <	4	1098	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.14, 6.55]
2 years				
29.2 Medium-long duration 2 to < 4 years	3	6950	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.61, 4.16]
29.3 Long duration 4+ years	4	6694	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.47, 0.97]
30 Stroke - subgroup by primary or secondary prevention	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
30.1 Primary prevention of cardiovascular disease (CVD)	4	6570	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.45, 1.11]
30.2 Secondary prevention of CVD	7	8172	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.59, 2.62]
31 Stroke - subgroup by baseline PUFA dose	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
31.1 Baseline total PUFA < 6% E	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
31.2 Baseline total PUFA 6 to < 11% E	3	7488	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.41, 3.59]
31.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31.4 Baseline total PUFA unclear	7	6408	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.51, 2.41]
32 Stroke - subgroup by	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
replacement	11		Nisk Ratio (Wi-11, Raildoni, 7770 Ci)	Subtotals only
32.1 PUFA replaced saturated	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
fats	1	3/30	rusk rutto (w 11, ruskuom, 7570 Ci)	1.50 [0.15, 1.11]
32.2 PUFA replaced	7	11742	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 0.99]
monounsaturated fats	,	11/ 12	14011 14110 (111 11) 14114 (11) 1511	0., 2 [0.,2, 0.,,]
32.3 PUFA replaced	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
carbohydrates			(), / / / //	[,]
32.4 PUFA replaced protein	1	393	Risk Ratio (M-H, Random, 95% CI)	4.88 [0.24, 100.89]
32.5 PUFA replaced unclear	2	574	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.02, 29.08]
33 Stroke - subgroup by sex	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
33.1 > 70% men	9	9354	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.56, 1.93]
33.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
33.3 men & women	1	4997	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.43, 1.05]
33.4 sex not reported	1	391	Risk Ratio (M-H, Random, 95% CI)	5.03 [0.24, 104.01]
34 Stroke - subgroup by age	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
34.1 Mean age < 50 years	1	458	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.15, 7.55]
34.2 Mean age 50 to < 65	5	2975	Risk Ratio (M-H, Random, 95% CI)	2.84 [1.05, 7.64]
years				
34.3 Mean age 65+ years	4	10918	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.94]
34.4 Mean age unclear	1	391	Risk Ratio (M-H, Random, 95% CI)	5.03 [0.24, 104.01]
35 Stroke - subgroup by statin use	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
35.1 < 50% on statins	9	9667	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.78]
35.2 50+% on statins	2	5075	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.07, 3.40]

36 Stroke - subgroup by intervention type	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
36.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.92, 12.04]
36.2 Supplemental foods &	3	10680	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.49, 0.96]
diet provided	3	10000	rusk ratio (ivi 11, random, 7570 Ci)	0.00 [0.17, 0.70]
36.3 Supplements (capsules &	5	1178	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.25, 5.62]
unusual foods)		11/0	rusk ratio (ivi 11, random, 7570 Ci)	1.10 [0.2), 7.02]
36.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.32, 8.62]
37 Stroke - subgroup by fatal &	11	~,-	Risk Ratio (M-H, Random, 95% CI)	Subtotals only
non fatal	11		rusic rutto (ivi 11, rumuom, 77,70 Oi)	ouototais omy
37.1 Fatal stroke	4	6534	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.38, 1.60]
37.2 Non-fatal stroke	2	1084	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.09, 2.51]
37.3 Only combined fatal &	6	7970	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.56, 4.07]
non fatal data provided		, , , ,	, , , , , , , , , , , , , , , , , , , ,	
38 Stroke - subgroup by ischaemic	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
& haemorrhagic			, , , , , , , , , , , , , , , , , , , ,	,,
38.1 Ischaemic stroke	3	2762	Risk Ratio (M-H, Random, 95% CI)	4.66 [1.00, 21.63]
38.2 Haemorrhagic stroke	3	2762	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.48, 7.85]
38.3 Only combined	8	11980	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.50, 0.97]
ischaemic and haemorrhagic				
data provided				
39 MAJOR ADVERSE	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
CARDIAC &				
CEREBROVASCULAR				
EVENTS (MACCEs)				
40 MACCEs - SA	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
40.1 Low risk of bias for	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
allocation concealment				
40.2 Low risk of bias for	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
attention				
40.3 Low risk of bias for	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
compliance				
40.4 Low summary risk of	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
bias				
40.5 Trials registry or pre-	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
2010				
40.6 No industry funding	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
40.7 Randomised 100+	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
participants				
40.8 Randomised 250+	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
participants				
41 MACCEs - SA fixed-effect	2	2879	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.04]
42 MACCEs - subgroup by PUFA	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
dose				
42.1 total PUFA < 1.0% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
42.2 total PUFA 1.0 to < 2.	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
0% E				
42.3 total PUFA 2.0 to < 5.	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
0% E				
42.4 total PUFA > 5.0% E	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]

43 MACCEs - subgroup by duration	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
43.1 Medium duration 1 to < 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
43.2 Medium-long duration 2 to < 4 years	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
43.3 Long duration 4+ years 44 MACCEs - subgroup	1 2	846 2879	Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93] 0.84 [0.59, 1.20]
by primary or secondary prevention			,	
44.1 Primary prevention of CVD	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
44.2 Secondary prevention of CVD	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
45 MACCEs - subgroup by baseline PUFA dose	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
45.1 Baseline total PUFA < 6% E	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
45.2 Baseline total PUFA 6 to < 11% E	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
45.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
45.4 Baseline total PUFA unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
46 MACCEs - subgroup by replacement	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
46.1 PUFA replaced saturated fats	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
46.2 PUFA replaced monounsaturated fats	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
46.3 PUFA replaced carbohydrates	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
46.4 PUFA replaced protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
46.5 PUFA replaced unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47 MACCEs - subgroup by sex	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
47.1 > 70% men	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
47.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.3 men & women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.4 sex not reported	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
48 MACCEs - subgroup by age	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
48.1 Mean age < 50 years	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0\ [0.0,\ 0.0]$
48.2 Mean age 50 to < 65	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
years				
48.3 Mean age 65+ years	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
49 MACCEs - subgroup by statin use	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
49.1 < 50% on statins	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
49.2 50+% on statins	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50 MACCEs - subgroup by intervention type	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
50.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]

0.69 [0.51, 0.93]
0.0 [0.0, 0.0]
0.0 [0.0, 0.0]

Comparison 2. Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CARDIOVASCULAR MORTALITY	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
2 Cardiovascular mortality - SA	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Low risk of bias for allocation concealment	6	6031	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.85, 1.38]
2.2 Low risk of bias for attention	9	11774	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.69, 1.07]
2.3 Low risk of bias for compliance	8	4142	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.49]
2.4 Low summary risk of bias	3	5431	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.77, 1.83]
2.5 Trials registry or pre-2010	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
2.6 No industry funding	7	1744	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.79, 1.79]
2.7 Randomised 100+ participants	13	14895	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.80, 1.28]
2.8 Randomised 250+ participants	7	13966	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
3 Cardiovascular mortality - SA fixed-effect	16	15107	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.88, 1.16]
4 Cardiovascular mortality - subgroup by PUFA dose	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
4.1 total PUFA < 1.0% E	5	1054	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.38, 1.51]
4.2 total PUFA 1.0 to < 2.0% E	3	9954	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.30]
4.3 total PUFA 2.0 to < 5.0% E	3	2246	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.96, 1.62]
4.4 total PUFA > 5.0% E	5	1853	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.62, 1.63]
5 Cardiovascular mortality - subgroup by duration	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
5.1 Medium duration 1 to <2 years	5	974	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.39, 1.67]
5.2 Medium-long duration 2 to < 4 years	6	7337	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.88, 1.36]
5.3 Long duration 4+ years	5	6796	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.55]
6 Cardiovascular mortality - subgroup by primary or secondary prevention	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
6.1 Primary prevention of cardiovascular disease (CVD)	7	6412	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.41]

6.2 Secondary prevention of	9	8695	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.92, 1.36]
CVD 7 Cardiovascular mortality -	16	15107	Diels Datio (M. H. Dandom, 050/, CI)	1 02 [0 92 1 26]
subgroup by baseline PUFA	10	1310/	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
7.1 Baseline total PUFA < 6% E	2	982	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.97]
7.2 Baseline total PUFA 6 to < 11% E	4	7621	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.07, 1.62]
7.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Baseline total PUFA unclear	10	6504	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.16]
8 Cardiovascular mortality - subgroup by replacement	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 PUFA replaced saturated fats	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.54]
8.2 PUFA replaced	8	11874	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.30]
monounsaturated fats				
8.3 PUFA replaced carbohydrates	4	425	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.30, 4.71]
8.4 PUFA replaced protein	2	529	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.66, 1.77]
8.5 PUFA replaced unclear	3	436	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.07, 1.37]
9 Cardiovascular mortality - subgroup by sex	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
9.1 > 70% men	10	9623	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.78, 1.27]
9.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 men & women	5	5430	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.30, 2.47]
9.4 sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.41, 5.84]
10 Cardiovascular mortality -	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
subgroup by age				
10.1 Mean age < 50 years	1	458	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.99, 2.55]
10.2 Mean age 50 to < 65 years	8	3149	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.95, 1.48]
10.3 Mean age 65+ years	6	11398	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.09]
10.4 Mean age unclear	1	102	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.60]
11 Cardiovascular mortality - subgroup by statin use	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
11.1 < 50% on statins	11	9416	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.40]
11.2 50+% on statins	3	5153	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.22]
11.3 Percentage on statins unclear	2	538	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.47, 2.54]
12 Cardiovascular mortality - subgroup by intervention type	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
12.1 Dietary advice	4	2404	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.42, 3.12]
12.2 Supplemental foods & diet provided	3	10680	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.66, 1.19]
12.3 Supplements (capsules & unusual foods)	7	1172	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.42, 1.40]
12.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.87, 1.95]

13 CARDIOVASCULAR EVENTS	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
14 CVD events - SA	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Low risk of bias for	11	8714	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.08]
allocation concealment		-,	(, , , , , , , , , , , , ,	, , [,]
14.2 Low risk of bias for	16	14111	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.72, 0.97]
attention			,	
14.3 Low risk of bias for	8	5697	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.14]
compliance			,	
14.4 Low summary risk of	6	7014	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.83, 1.67]
bias			,	,
14.5 Trials registry or pre-	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
2010			(, , , , , , , , , , , , ,	, [,,]
14.6 No industry funding	5	2440	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.67, 1.44]
14.7 Randomised 100+	18	17587	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.77, 1.00]
participants			, , ,	
14.8 Randomised 250+	11	16524	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.85, 1.02]
participants			,	, , ,
15 CVD events - SA fixed-effect	21	17799	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.98]
16 CVD events - subgroup by	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
PUFA dose				
16.1 total PUFA < 1.0% E	7	1563	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.42, 0.96]
16.2 total PUFA 1.0 to < 2.	5	10468	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.03]
0% E				
16.3 total PUFA 2.0 to < 5.	3	2224	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.09]
0% E				
16.4 total PUFA > 5.0% E	6	3544	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.29]
17 CVD events - subgroup by	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
duration				
17.1 Medium duration 1 to <	11	3175	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.47, 0.99]
2 years				
17.2 Medium-long duration 2	6	7930	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
to < 4 years				
17.3 Long duration 4+ years	4	6694	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]
18 CVD events - subgroup	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
by primary or secondary				
prevention				
18.1 Primary prevention of	10	8893	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
CVD				
18.2 Secondary prevention of	11	8906	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.05]
CVD				
19 CVD events - subgroup by	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
baseline PUFA dose				
19.1 Baseline total PUFA <	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
6% E				
19.2 Baseline total PUFA 6 to	4	8214	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.85, 1.22]
< 11% E				
19.3 Baseline total PUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11+% E				_
19.4 Baseline total PUFA	15	7672	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.69, 0.98]
unclear				

20 CVD events - subgroup by replacement	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 PUFA replaced saturated fats	6	5523	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.14]
20.2 PUFA replaced monounsaturated fats	12	13605	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.08]
20.3 PUFA replaced carbohydrates	2	780	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.70, 2.01]
20.4 PUFA replaced protein	2	1119	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.62, 1.07]
20.5 PUFA replaced unclear	6	1042	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.29, 0.95]
21 CVD events - subgroup by sex	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
21.1 > 70% men	12	10798	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.00]
21.2 > 70% women	1	140	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.08, 44.38]
21.3 men & women	6	6416	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.68, 1.18]
21.4 sex not reported	2	445	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.80, 2.20]
22 CVD events - subgroup by age	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
22.1 Mean age < 50 years	4	2020	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.05, 2.61]
22.2 Mean age 50 to < 65	9	3264	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.08]
years				
22.3 Mean age 65+ years	7	12124	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.78, 0.96]
22.4 Mean age unclear	1	391	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.54, 4.83]
23 CVD events - subgroup by statin use	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
23.1 < 50% on statins	16	11518	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
23.2 50+% on statins	3	5153	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.43, 1.25]
23.3 Percentage on statins	2	1128	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.53, 1.21]
unclear				
24 CVD events - subgroup by	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
intervention type				
24.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.09]
24.2 Supplemental foods & diet provided	5	12473	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.99]
24.3 Supplements (capsules & unusual foods)	13	2442	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.54, 1.04]
24.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.57, 2.13]
25 CORONARY HEART DISEASE (CHD) MORTALITY	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
26 CHD mortality - SA	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 Low risk of bias for allocation concealment	3	5359	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.68, 1.25]
26.2 Low risk of bias for attention	8	6777	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.70, 1.18]
26.3 Low risk of bias for compliance	4	3053	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.10]
26.4 Low summary risk of bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.28]
26.5 Trials registry or pre- 2010	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
26.6 No industry funding	2	522	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.25, 2.58]

26.7 Randomised 100+ participants	7	8676	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.06]
26.8 Randomised 250+ participants	4	8118	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.08]
27 CHD mortality - SA fixed-effect	9	8810	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
28 CHD mortality - subgroup by PUFA dose	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
28.1 total PUFA < 1.0% E	3	840	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.35, 1.59]
28.2 total PUFA 1.0 to < 2. 0% E	2	4957	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.41, 1.76]
28.3 total PUFA 2.0 to < 5. 0% E	2	2113	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.74, 1.10]
28.4 total PUFA > 5.0% E	2	900	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.60, 1.78]
29 CHD mortality - subgroup by duration	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
29.1 Medium duration 1 to < 2 years	3	760	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.34, 1.83]
29.2 Medium-long duration 2 to < 4 years	5	7204	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.07]
29.3 Long duration 4+ years	1	846	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.57, 1.75]
30 CHD mortality - subgroup by primary or secondary prevention	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
30.1 Primary prevention of CVD	2	966	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.30, 2.34]
30.2 Secondary prevention of CVD	7	7844	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.06]
31 CHD mortality - subgroup by baseline PUFA dose	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
31.1 Baseline total PUFA < 6% E	1	846	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.57, 1.75]
31.2 Baseline total PUFA 6 to < 11% E	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
31.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31.4 Baseline total PUFA unclear	7	5931	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.19]
32 CHD mortality - subgroup by replacement	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1 PUFA replaced saturated fats	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.10]
32.2 PUFA replaced monounsaturated fats	6	6419	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.71, 1.21]
32.3 PUFA replaced carbohydrates	1	54	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.18, 19.29]
32.4 PUFA replaced protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
32.5 PUFA replaced unclear	2	358	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.02, 1.65]
33 CHD mortality - subgroup by sex	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
33.1 > 70% men	7	8636	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]

33.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
33.3 men & women	1	120	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 4.05]
33.4 sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.18, 19.29]
34 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
age				
34.1 Mean age < 50 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
34.2 Mean age 50 to < 65	5	2487	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.08]
years				
34.3 Mean age 65+ years	4	6323	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.71, 1.23]
35 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
statin use				
35.1 < 50% on statins	6	3333	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.75, 1.08]
35.2 50+% on statins	2	5075	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.65, 1.26]
35.3 Percentage on statins unclear	1	402	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.41, 2.49]
	0	0010	D:-l- D:- (M II D l 050/ CI)	0.01 [0.79 1.07]
36 CHD mortality - subgroup by intervention type	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
36.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
36.2 Supplemental foods &	2	5683	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.71, 1.25]
diet provided	2	7003	Risk Ratio (191-11, Randoni, 7570 Ci)	0.74 [0./1, 1.27]
36.3 Supplements (capsules &	6	1094	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.36, 1.43]
unusual foods)	O	1071	rusk ratio (ivi 11, rushuom, 7570 Ci)	0.72 [0.30, 1.13]
36.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
37 MYOCARDIAL	15	15609	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.99]
INFARCTION (MI) - fatal			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	[, .,,]
and non fatal				
38 SUDDEN CARDIAC	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.50, 1.29]
DEATH (SCD)				
39 ATRIAL FIBRILLATION	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
(AF) & ARRHYTHMIAS				
(including AF, ventricular				
tachycardia (VT), ventricular				
fibrillation(VF)	,	070	Dil Di (MILD I 1050/ CD)	0.01 [0.65 1.01]
39.1 Recurrent arrhythmia	4	979	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.01]
39.2 New arrhythmia 40 AF - SA	7 11	10713	Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI)	1.01 [0.70, 1.46] Subtotals only
40.1 Low risk of bias for	7	6679	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.88]
allocation concealment	/	00/)	Risk Ratio (191-11, Randoni, 7570 Ci)	0./4 [0.03, 0.00]
40.2 Low risk of bias for	10	11514	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.13]
attention	10	11)14	Ratio (Wi-11, Randoni, 7770 Ci)	0.70 [0.72, 1.13]
40.3 Low risk of bias for	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
compliance	Ü	v	14011 14110 (111 111, 14114 0111, 7570 01)	0.0 [0.0, 0.0]
40.4 Low summary risk of	3	5368	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.12]
bias			, , , , , , , , , , , , , , , , , , , ,	
40.5 Trials registry or pre-	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
2010			, ,	
40.6 No industry funding	2	601	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.88]
40.7 Randomised 100+	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
participants				
40.8 Randomised 250+	6	10842	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.28]
participants				

41 AF - SA fixed-effect	11	11692	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 1.00]
41.1 Recurrent arrhythmia	4	979	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
41.2 New arrhythmia	7	10713	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]
42 AF - subgroup by PUFA dose	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
42.1 total PUFA < 1.0% E	7	1839	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
42.2 total PUFA 1.0 to < 2.	4	9853	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.60]
0% E	_	, , , ,		[,,]
42.3 total PUFA 2.0 to < 5.	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
0% E	Ü	Ü	Tubic Futio (111 Fig. Futionity 9976 CI)	0.0 [0.0, 0.0]
42.4 total PUFA 5.0+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
43 AF - subgroup by duration	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
43.1 Medium duration 1 to <	8	2153	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.65, 0.83]
2 years	Ü	21)3	Tubic Futio (111 Fig. Futionity 9976 CI)	0.7 1 [0.05, 0.05]
43.2 Medium-long duration 2	2	5037	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.66, 1.36]
to < 4 years	2	3037	rusk reacto (141 11, realidotti, 7576 CI)	0.77 [0.00, 1.30]
43.3 Long duration 4+ years	1	4502	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.98, 1.79]
44 AF - subgroup by primary or	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
secondary prevention	11	110)2	Ratio (Wi-11, Randolli, 7)/6 Ci)	0.07 [0.72, 1.00]
44.1 Primary prevention of	5	5743	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.99, 1.79]
CVD)	3/43	Risk Ratio (Wi-11, Randolli, 9)70 Ci)	1.33 [0.33, 1./3]
	6	50/0	Diala Davia (M. I.I. Davida va 050/ CI)	0.00 [0.67, 0.06]
44.2 Secondary prevention of CVD	6	5949	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.96]
	1.1	11/02	D' I D .' (MII D . I . OSOV CI)	0.07 [0.72 1.07]
45 Atrial fibrillation - subgroup by	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
baseline PUFA dose	0	0	D' I D ' (MAIL D I DOGN CI)	
45.1 Baseline total PUFA <	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6% E	_	(500	DIL D. I. (MALL D. J. 1950) CD	4 22 [2 22 4 72]
45.2 Baseline total PUFA 6 to	1	4502	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.98, 1.79]
< 11% E				
45.3 Baseline total PUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11+% E				
45.4 Baseline total PUFA	10	7190	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.95]
unclear				
46 AF - subgroup by replacement	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
46.1 PUFA replaced saturated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
fats				
46.2 PUFA replaced	8	10804	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.14]
monounsaturated fats				
46.3 PUFA replaced	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
carbohydrates				
46.4 PUFA replaced protein	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
46.5 PUFA replaced unclear	3	888	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.64, 0.88]
47 Atrial fibrillation - subgroup by	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
sex				
47.1 > 70% men	6	6086	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 1.01]
47.2 > 70% women	1	140	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.08, 44.38]
47.3 men & women	3	5075	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.50, 1.93]
47.4 sex not reported	1	391	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.18, 21.99]
48 AF - subgroup by age	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
48.1 Mean age < 50 years	1	374	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.12, 72.40]
48.2 Mean age 50 to < 65	5	987	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.62, 1.23]
years				

48.3 Mean age 65+ years	4	9940	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.63, 1.15]
48.4 Mean age unclear	1	391	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.18, 21.99]
49 AF - subgroup by statin use	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
49.1 < 50% on statins	9	6453	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.68, 1.21]
49.2 50+% on statins	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
49.3 Percentage on statins	1	402	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.01]
unclear				
50 AF - subgroup by intervention	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
type				
50.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50.2 Supplemental foods &	2	9339	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.70]
diet provided				
50.3 Supplements (capsules &	9	2353	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.98]
unusual foods)				
50.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
51 ANGINA	7	2070	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.35, 1.16]
52 HEART FAILURE	7	25257	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.40, 1.36]
53 PERIPHERAL ARTERIAL	4	8937	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.81, 1.77]
DISEASE (PAD)				
54 REVASCULARISATION -	6	1182	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.40, 1.24]
angioplasty and/or coronary				
artery bypass grafting				
		·		·

Comparison 3. Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADIPOSITY - BODY	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
WEIGHT, kg				
2 Body weight, kg - SA	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Low risk of bias for	5	2586	Mean Difference (IV, Random, 95% CI)	1.72 [0.29, 3.15]
allocation concealment				
2.2 Low risk of bias for	7	4156	Mean Difference (IV, Random, 95% CI)	0.57 [0.08, 1.06]
attention				
2.3 Low risk of bias for	5	756	Mean Difference (IV, Random, 95% CI)	1.59 [-0.11, 3.28]
compliance				
2.4 Low summary risk of bias	4	2550	Mean Difference (IV, Random, 95% CI)	1.81 [0.23, 3.38]
2.5 Trials registry or pre-2010	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
2.6 No industry funding	6	2783	Mean Difference (IV, Random, 95% CI)	1.62 [0.11, 3.14]
2.7 Randomised 100+	8	6885	Mean Difference (IV, Random, 95% CI)	0.89 [0.41, 1.36]
participants				
2.8 Randomised 250+	5	6539	Mean Difference (IV, Random, 95% CI)	0.81 [0.34, 1.28]
participants				
3 Body weight, kg - SA fixed-effect	13	7100	Mean Difference (IV, Fixed, 95% CI)	1.08 [0.96, 1.21]
4 Body weight, kg - subgroup by	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
PUFA dose				
4.1 total PUFA < 1.0% E	2	287	Mean Difference (IV, Random, 95% CI)	1.78 [-1.46, 5.01]

4.2 total PUFA 1.0 to < 2.0% E	5	6079	Mean Difference (IV, Random, 95% CI)	0.74 [0.18, 1.30]
4.3 total PUFA 2.0 to < 5.0% E	3	210	Mean Difference (IV, Random, 95% CI)	1.47 [-3.60, 6.53]
4.4 total PUFA 5.0+% E	3	524	Mean Difference (IV, Random, 95% CI)	0.75 [-0.10, 1.60]
5 Body weight, kg - subgroup by	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
duration				
5.1 Medium duration 1 to < 2 years	6	502	Mean Difference (IV, Random, 95% CI)	0.47 [-0.20, 1.14]
5.2 Medium-long duration 2 to < 4 years	4	522	Mean Difference (IV, Random, 95% CI)	0.78 [-0.06, 1.62]
5.3 Long duration 4+ years	3	6076	Mean Difference (IV, Random, 95% CI)	0.90 [0.27, 1.54]
6 Body weight, kg - subgroup by primary or secondary prevention	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
6.1 Primary prevention of CVD	11	6864	Mean Difference (IV, Random, 95% CI)	0.76 [0.33, 1.19]
6.2 Secondary prevention of CVD	2	236	Mean Difference (IV, Random, 95% CI)	2.0 [-5.43, 9.43]
7 Body weight, kg - subgroup by baseline PUFA dose	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
7.1 Baseline total PUFA < 6% E	3	2339	Mean Difference (IV, Random, 95% CI)	2.37 [1.18, 3.56]
7.2 Baseline total PUFA 6 to < 11% E	5	4345	Mean Difference (IV, Random, 95% CI)	0.68 [0.21, 1.15]
7.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Baseline total PUFA unclear	5	416	Mean Difference (IV, Random, 95% CI)	0.18 [-0.68, 1.03]
8 Body weight, kg - subgroup by replacement	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 PUFA replaced saturated fats	3	248	Mean Difference (IV, Random, 95% CI)	0.59 [-5.15, 6.34]
8.2 PUFA replaced monounsaturated fats	4	4036	Mean Difference (IV, Random, 95% CI)	0.69 [0.15, 1.23]
8.3 PUFA replaced carbohydrates	5	2882	Mean Difference (IV, Random, 95% CI)	1.23 [0.27, 2.20]
8.4 PUFA replaced protein	4	660	Mean Difference (IV, Random, 95% CI)	1.56 [-0.64, 3.75]
8.5 unclear	2	85	Mean Difference (IV, Random, 95% CI)	0.08 [-0.80, 0.95]
9 Body weight, kg - subgroup by sex	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
9.1 > 70% men	4	408	Mean Difference (IV, Random, 95% CI)	3.14 [0.31, 5.98]
9.2 > 70% women	3	2253	Mean Difference (IV, Random, 95% CI)	0.78 [-0.60, 2.17]
9.3 men & women	5	4404	Mean Difference (IV, Random, 95% CI)	0.70 [0.22, 1.18]
9.4 sex not reported	1	35	Mean Difference (IV, Random, 95% CI)	-0.30 [-10.57, 9.97]
10 Body weight, kg - subgroup by age	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
10.1 Mean age < 50 years	2	79	Mean Difference (IV, Random, 95% CI)	0.21 [-1.12, 1.54]
10.2 Mean age 50 to < 65	9	2978	Mean Difference (IV, Random, 95% CI)	1.15 [0.12, 2.18]
years 10.3 Mean age 65+ years	2	4043	Mean Difference (IV, Random, 95% CI)	0.71 [0.16, 1.26]

11 Body weight, kg - subgroup by statin use	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
11.1 < 50% on statins	9	6522	Mean Difference (IV, Random, 95% CI)	0.69 [0.21, 1.17]
11.2 50+% on statins	2	130	Mean Difference (IV, Random, 95% CI)	2.70 [-2.43, 7.83]
11.3 Percentage on statins	2	448	Mean Difference (IV, Random, 95% CI)	1.88 [-1.08, 4.84]
unclear				
12 Body weight, kg - subgroup by intervention type	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
12.1 Dietary advice	4	2455	Mean Difference (IV, Random, 95% CI)	2.37 [1.19, 3.55]
12.2 Supplemental foods & diet provided	3	4078	Mean Difference (IV, Random, 95% CI)	0.71 [0.18, 1.25]
12.3 Supplements (capsules & unusual foods)	5	390	Mean Difference (IV, Random, 95% CI)	0.37 [-0.18, 0.91]
12.4 Any combination	1	177	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 ADIPOSITY - Body Mass Index (BMI), kg/m2	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
14 BMI, kg/m2 - SA	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Low risk of bias for	4	3894	Mean Difference (IV, Random, 95% CI)	0.37 [-0.15, 0.88]
allocation concealment				
14.2 Low risk of bias for attention	6	2259	Mean Difference (IV, Random, 95% CI)	0.15 [-0.12, 0.42]
14.3 Low risk of bias for compliance	3	526	Mean Difference (IV, Random, 95% CI)	0.96 [-0.86, 2.78]
14.4 Low summary risk of bias	4	3894	Mean Difference (IV, Random, 95% CI)	0.37 [-0.15, 0.88]
14.5 Trials registry or pre- 2010	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
14.6 No industry funding	2	2539	Mean Difference (IV, Random, 95% CI)	0.28 [-0.70, 1.26]
14.7 Randomised 100+	7	4738	Mean Difference (IV, Random, 95% CI)	0.16 [-0.09, 0.41]
participants				
14.8 Randomised 250+ participants	4	4331	Mean Difference (IV, Random, 95% CI)	0.21 [-0.04, 0.46]
15 BMI, kg/m2 - SA fixed-effect	8	4798	Mean Difference (IV, Fixed, 95% CI)	0.27 [0.20, 0.35]
16 BMI, kg/m2 - subgroup by PUFA dose	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
16.1 total PUFA < 1.0% E	2	193	Mean Difference (IV, Random, 95% CI)	0.01 [-0.17, 0.18]
16.2 total PUFA 1.0 to < 2.	5	4234	Mean Difference (IV, Random, 95% CI)	0.26 [-0.03, 0.55]
0% E				
16.3 total PUFA 2.0 to < 5. 0% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.4 total PUFA 5.0+% E	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
17 BMI, kg/m2 - subgroup by	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
duration				
17.1 Medium duration 1 to < 2 years	3	407	Mean Difference (IV, Random, 95% CI)	0.21 [-1.40, 1.81]
17.2 Medium-long duration 2 to < 4 years	2	1320	Mean Difference (IV, Random, 95% CI)	0.16 [-0.03, 0.34]
17.3 Long duration 4+ years	3	3071	Mean Difference (IV, Random, 95% CI)	0.22 [-0.12, 0.55]
18 BMI, kg/m2 - subgroup	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
by primary or secondary prevention	O	7/ 70	rican Difference (18, Kandoni, 2270 CI)	0.17 [-0.00, 0.42]

18.1 Primary prevention of CVD	5	3034	Mean Difference (IV, Random, 95% CI)	0.30 [-0.09, 0.69]
18.2 Secondary prevention of CVD	3	1764	Mean Difference (IV, Random, 95% CI)	0.03 [-0.13, 0.19]
19 BMI, kg/m2 - subgroup by baseline PUFA dose	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
19.1 Baseline total PUFA < 6% E	2	2347	Mean Difference (IV, Random, 95% CI)	-0.26 [-2.51, 1.99]
19.2 Baseline total PUFA 6 to < 11% E	2	903	Mean Difference (IV, Random, 95% CI)	0.10 [-0.27, 0.47]
19.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
19.4 Baseline total PUFA unclear	4	1548	Mean Difference (IV, Random, 95% CI)	0.16 [-0.16, 0.48]
20 BMI, kg/m2 - subgroup by replacement	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 PUFA replaced saturated fats	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
20.2 PUFA replaced monounsaturated fats	5	2391	Mean Difference (IV, Random, 95% CI)	0.14 [-0.11, 0.39]
20.3 PUFA replaced carbohydrates	2	2347	Mean Difference (IV, Random, 95% CI)	-0.26 [-2.51, 1.99]
20.4 PUFA replaced protein	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.5 PUFA replaced unclear	1	60	Mean Difference (IV, Random, 95% CI)	1.0 [-1.18, 3.18]
21 BMI, kg/m2 - subgroup by sex	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
21.1 > 70% men	3	1764	Mean Difference (IV, Random, 95% CI)	0.03 [-0.13, 0.19]
21.2 > 70% women	2	2347	Mean Difference (IV, Random, 95% CI)	-0.26 [-2.51, 1.99]
21.3 men & women	3	687	Mean Difference (IV, Random, 95% CI)	0.31 [-0.08, 0.71]
22 BMI, kg/m2 - subgroup by age	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
22.1 Mean age < 50 years	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
22.2 Mean age 50 to < 65	5	2635	Mean Difference (IV, Random, 95% CI)	0.38 [-0.42, 1.18]
years			,	, ,
22.3 Mean age 65+ years	2	1792	Mean Difference (IV, Random, 95% CI)	0.21 [-0.04, 0.47]
23 BMI, kg/m2 - subgroup by statin use	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
23.1 < 50% on statins	6	3443	Mean Difference (IV, Random, 95% CI)	0.12 [-0.17, 0.42]
23.2 50+% on statins	2	1355	Mean Difference (IV, Random, 95% CI)	1.19 [-1.19, 3.56]
23.3 Percentage on statins unclear	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
24 BMI, kg/m2 - subgroup by intervention type	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
24.1 Dietary advice	1	2168	Mean Difference (IV, Random, 95% CI)	0.80 [0.30, 1.30]
24.2 Supplemental foods &	2	1792	Mean Difference (IV, Random, 95% CI)	0.21 [-0.04, 0.47]
diet provided				
24.3 Supplements (capsules & unusual foods)	4	467	Mean Difference (IV, Random, 95% CI)	0.33 [-0.99, 1.64]
24.4 Any combination	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
25 Adiposity - waist circumference,	3	1298	Mean Difference (IV, Random, 95% CI)	0.25 [-0.32, 0.83]
cm				
26 Adiposity - % body fat	2	309	Mean Difference (IV, Random, 95% CI)	1.90 [-1.41, 5.21]
27 Adiposity - body fat, kg	1	214	Mean Difference (IV, Random, 95% CI)	0.0 [-1.12, 1.12]

28 Serum TOTAL CHOLESTEROL (TC,	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
mmoL/L)				
29 TC, mmoL/L - SA	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 Low risk of bias for allocation concealment	10	3548	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.36, 0.03]
29.2 Low risk of bias for	19	4830	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.23, 0.04]
attention				
29.3 Low risk of bias for compliance	15	5642	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.39, -0.14]
29.4 Low summary risk of bias	7	3204	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.46, 0.01]
29.5 Trials registry or pre- 2010	25	7808	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.24, -0.03]
29.6 No industry funding	11	2570	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.39, 0.01]
29.7 Randomised 100+ participants	19	7711	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.27, -0.05]
29.8 Randomised 250+ participants	9	6348	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.30, -0.05]
30 TC, mmoL/L - SA fixed-effect	27	8072	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.26, -0.18]
31 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
PUFA dose				
31.1 total PUFA < 1.0% E	4	480	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.15, 0.13]
31.2 total PUFA 1.0 to < 2. 0% E	8	2170	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.16, 0.04]
31.3 total PUFA 2.0 to < 5. 0% E	4	1857	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.31, 0.25]
31.4 total PUFA 5.0+% E	11	3565	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.45, -0.10]
32 TC, mmoL/L - subgroup by duration	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
32.1 Medium duration 1 to < 2 years	13	2168	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.30, 0.08]
32.2 Medium-long duration 2 to < 4 years	9	4012	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.19, 0.05]
32.3 Long duration 4+ years	5	1892	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.40, -0.06]
33 TC, mmoL/L - subgroup by primary or secondary prevention	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
33.1 Primary prevention of CVD	17	4006	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.26, 0.02]
33.2 Secondary prevention of CVD	10	4066	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.24, -0.00]
34 TC, mmoL/L - subgroup by baseline PUFA dose	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
34.1 Baseline total PUFA < 6% E	6	2347	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.56, -0.09]
34.2 Baseline total PUFA 6 to < 11% E	7	3394	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.21, 0.04]
34.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

34.4 Baseline total PUFA unclear	14	2331	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.16, 0.04]
35 TC, mmoL/L - subgroup by replacement	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
35.1 PUFA replaced saturated fats	8	4572	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.50, -0.14]
35.2 PUFA replaced monounsaturated fats	13	4500	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.33, -0.00]
35.3 PUFA replaced carbohydrates	9	1394	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.23, 0.10]
35.4 PUFA replaced protein	4	862	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.30, 0.24]
35.5 PUFA replaced unclear	3	238	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.29, 0.12]
36 TC, mmoL/L - subgroup by sex	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
36.1 > 70% men	15	6393	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.30, -0.01]
36.2 > 70% women	2	251	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.64, 0.61]
36.3 men & women	8	1367	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.22, 0.01]
36.4 sex not reported	2	61	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.80, 0.73]
37 TC, mmoL/L - subgroup by age	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
37.1 Mean age < 50 years	5	1713	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.59, -0.02]
37.2 Mean age 50 to < 65	15	3250	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.06]
years	-2	0_0		, [, ,]
37.3 Mean age 65+ years	4	2885	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.21, 0.00]
37.4 Mean age unclear	3	224	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.52, 0.20]
38 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
statin use	,		(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
38.1 < 50% on statins	20	5818	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.28, -0.03]
38.2 50+% on statins	5	1604	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.11, 0.08]
38.3 Percentage on statins	2	650	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.35, 0.15]
unclear	_	0,0	Tream Direction (17) rundom, 7570 G2)	0.10 [0.55, 0.15]
39 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
intervention type	-/	00,2	Tream Direction (17) rundom, 7570 G2)	0.12 [0.23, 0.02]
39.1 Dietary advice	4	2019	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.15]
39.2 Supplemental foods &	8	4264	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.37, -0.01]
diet provided	Ü	1201	Tream Directives (17, random, 7570 Ci)	0.17 [0.37, 0.01]
39.3 Supplements (capsules & unusual foods)	11	934	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.19, 0.02]
39.4 Any combination	4	855	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.34, 0.29]
40 Serum fasting	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
TRIGLYCERIDE (TG, mmoL/L)	20	3707	ivican Difference (17, Randoni, 7)/0 Ci)	-0.12 [-0.20, -0.04]
41 TG, mmoL/L - SA	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
41.1 Low risk of bias for	9	2686	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.28, -0.06]
allocation concealment				
41.2 Low risk of bias for attention	15	3108	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.20, -0.01]
41.3 Low risk of bias for compliance	8	1175	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.19, 0.03]
41.4 Low summary risk of	5	2050	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.26, -0.03]
bias				•

41.5 Trials registry or pre- 2010	19	3715	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.21, -0.05]
41.6 No industry funding	8	1196	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.25, 0.09]
41.7 Randomised 100+	14	3637	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.19, -0.06]
participants			(, , , , , , , , , , , , , , , , , , ,	
41.8 Randomised 250+	5	2472	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.27, -0.07]
participants			(, , , , , , , , , , , , , , , , , , ,	, [, ,,]
42 TG, mmoL/L - SA fixed-effect	20	3905	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.16, -0.06]
43 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
PUFA dose			, , , , , , , , , , , , , , , , , , , ,	
43.1 total PUFA < 1.0% E	5	815	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.37, -0.02]
43.2 total PUFA 1.0 to < 2.	7	2091	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.15, -0.01]
0% E				
43.3 total PUFA 2.0 to < 5.	3	149	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.91, 0.75]
0% E				
43.4 total PUFA 5.0+% E	5	850	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.20, 0.06]
44 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
duration				
44.1 Medium duration 1 to <	10	1246	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.28, 0.04]
2 years				
44.2 Medium-long duration 2	7	1787	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.18, 0.07]
to < 4 years				
44.3 Long duration 4+ years	3	872	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.23, -0.03]
45 TG, mmoL/L - subgroup	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
by primary or secondary				
prevention				
45.1 Primary prevention of	14	1831	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.21, 0.01]
CVD				
45.2 Secondary prevention of	6	2074	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.22, 0.00]
CVD				
46 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
baseline PUFA dose				
46.1 Baseline total PUFA <	3	350	Mean Difference (IV, Random, 95% CI)	0.01 [-0.16, 0.17]
6% E				
46.2 Baseline total PUFA 6 to	6	1195	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.23, -0.06]
< 11% E				
46.3 Baseline total PUFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11+% E				
46.4 Baseline total PUFA	11	2360	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.27, 0.01]
unclear				
47 TG, mmoL/L - subgroup by	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
replacement				
47.1 PUFA replaced saturated	4	719	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.09]
fats				
47.2 PUFA replaced	8	2448	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.24, -0.08]
monounsaturated fats				
47.3 PUFA replaced	7	848	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.23, 0.14]
carbohydrates				
47.4 PUFA replaced protein	2	171	Mean Difference (IV, Random, 95% CI)	0.12 [-0.26, 0.51]
47.5 PUFA replaced unclear	3	499	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.50, 0.21]

48 TG, mmoL/L - subgroup by sex	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
48.1 > 70% men	11	2796	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.23, 0.03]
48.2 > 70% women	2	250	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.20, 0.13]
48.3 men & women	6	824	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.28, -0.09]
48.4 sex not reported	1	35	Mean Difference (IV, Random, 95% CI)	0.30 [-0.39, 0.99]
49 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
age	20	370)	ivican Difference (1 v, Random, 7) /0 Ci)	-0.12 [-0.20, -0.04]
49.1 Mean age < 50 years	3	565	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.26, 0.04]
49.2 Mean age 50 to < 65	13	1662	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.26, -0.03]
years				
49.3 Mean age 65+ years	2	1528	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.17, 0.01]
49.4 Mean age unclear	2	150	Mean Difference (IV, Random, 95% CI)	0.14 [-0.68, 0.96]
50 TG, mmoL/L - subgroup by statin use	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
50.1 < 50% on statins	15	2239	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.24, -0.04]
50.2 50+% on statins	4	1530	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.15, 0.08]
50.3 Percentage on statins	1	136	Mean Difference (IV, Random, 95% CI)	0.04 [-0.42, 0.50]
unclear		-00		**** [***=, **, **]
51 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
intervention type	4	339	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.37, 0.00]
51.1 Dietary advice			Mean Difference (IV, Random, 95% CI)	-
51.2 Supplemental foods & diet provided	4	1753	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.12, 0.03]
51.3 Supplements (capsules & unusual foods)	9	1140	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.35, -0.10]
51.4 Any combination	3	673	Mean Difference (IV, Random, 95% CI)	0.12 [-0.22, 0.46]
52 Serum HIGH DENSITY	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
LIPOPROTEIN (HDL, mmoL/L)	10	10, 1	Treat Difference (11, random, 77, 70 Gz)	0.01 [0.02, 0.01]
53 HDL, mmoL/L - SA	18		Mean Difference (IV, Random, 95% CI)	Subtotals only
53.1 Low risk of bias for	8	1968	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
allocation concealment	o	1908	Wealt Difference (1V, Kandolli, 9)70 C1)	-0.01 [-0.04, 0.01]
53.2 Low risk of bias for	13	2641	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
attention				
53.3 Low risk of bias for compliance	8	2410	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.02, 0.02]
53.4 Low summary risk of	4	1592	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
bias	_	-277		[,]
53.5 Trials registry or pre-	16	4410	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
2010	_		M. Diff. (HAD I ago, CI)	0.04 [0.0 / 0.05]
53.6 No industry funding	7	717	Mean Difference (IV, Random, 95% CI)	0.01 [-0.04, 0.05]
53.7 Randomised 100+	11	4332	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
participants				
53.8 Randomised 250+	4	3394	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
participants				
54 HDL, mmoL/L - SA	18	4674	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
fixed-effect				
55 HDL, mmoL/L - subgroup by PUFA dose	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
55.1 total PUFA < 1.0% E	3	347	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.09]
PUFA dose				

55.2 total PUFA 1.0 to < 2. 0% E	8	2166	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
55.3 total PUFA 2.0 to < 5. 0% E	4	1864	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.02]
55.4 total PUFA 5.0+% E	3	297	Mean Difference (IV, Random, 95% CI)	0.05 [-0.04, 0.14]
56 HDL, mmoL/L - subgroup by	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
duration			, : ,	
56.1 Medium duration 1 to < 2 years	9	852	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.04, 0.04]
56.2 Medium-long duration 2 to < 4 years	8	3504	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
56.3 Long duration 4+ years	1	318	Mean Difference (IV, Random, 95% CI)	0.03 [-0.02, 0.09]
57 HDL, mmoL/L - subgroup	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
by primary or secondary prevention				
57.1 Primary prevention of CVD	12	1402	Mean Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.04]
57.2 Secondary prevention of CVD	6	3272	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
58 HDL, mmoL/L - subgroup by baseline PUFA dose	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
58.1 Baseline total PUFA < 6% E	3	350	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.11, 0.09]
58.2 Baseline total PUFA 6 to < 11% E	6	2454	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.02]
58.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
58.4 Baseline total PUFA unclear	9	1870	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
59 HDL, mmoL/L - subgroup by replacement	18		Mean Difference (IV, Random, 95% CI)	Subtotals only
59.1 PUFA replaced saturated fats	4	1976	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
59.2 PUFA replaced monounsaturated fats	6	1857	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
59.3 PUFA replaced carbohydrates	6	754	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.06, 0.03]
59.4 PUFA replaced protein	2	171	Mean Difference (IV, Random, 95% CI)	0.04 [-0.06, 0.14]
59.5 PUFA replaced unclear	3	238	Mean Difference (IV, Random, 95% CI)	0.05 [-0.04, 0.14]
60 HDL, mmoL/L - subgroup by sex	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
60.1 > 70% men	10	3660	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
60.2 > 70% women	2	251	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.21, 0.17]
60.3 men & women	5	728	Mean Difference (IV, Random, 95% CI)	0.03 [-0.02, 0.07]
60.4 sex not reported	1	35	Mean Difference (IV, Random, 95% CI)	0.10 [-0.17, 0.37]
61 HDL, mmoL/L - subgroup by age	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
61.1 Mean age < 50 years	2	108	Mean Difference (IV, Random, 95% CI)	0.05 [-0.13, 0.23]
61.2 Mean age 50 to < 65 years	12	2910	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
61.3 Mean age 65+ years	2	1528	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.04, 0.03]

(1 /) (2	120	M Diff (NAD 1 050/ CD)	0.01.[0.00.0.10]
61.4 Mean age unclear	2	128	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.10]
62 HDL, mmoL/L - subgroup by	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
statin use	10	202/	M D'M (MAD 1 050) CIV	[20 0 2 0 0 1 0 0 0
62.1 < 50% on statins	12	2934 1604	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.02]
62.2 50+% on statins	5		Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
62.3 Percentage on statins unclear	1	136	Mean Difference (IV, Random, 95% CI)	0.03 [-0.08, 0.14]
63 HDL, mmoL/L - subgroup by intervention type	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
63.1 Dietary advice	4	1959	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
63.2 Supplemental foods &	4	1753	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
diet provided			D.M. (711 D. 1	
63.3 Supplements (capsules & unusual foods)	8	746	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.05, 0.04]
63.4 Any combination	2	216	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.06]
64 Serum LOW DENSITY	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
LIPOPROTEIN (LDL,				
mmoL/L)	1.5		M D'M (MAD 1 050) CIV	6.111
65 LDL, mmoL/L - SA	15	1015	Mean Difference (IV, Random, 95% CI)	Subtotals only
65.1 Low risk of bias for allocation concealment	6	1915	Mean Difference (IV, Random, 95% CI)	0.04 [-0.03, 0.10]
65.2 Low risk of bias for attention	11	2566	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.07]
65.3 Low risk of bias for	5	1009	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.06]
compliance				
65.4 Low summary risk of bias	4	1506	Mean Difference (IV, Random, 95% CI)	0.02 [-0.06, 0.09]
65.5 Trials registry or pre-	13	3098	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.07]
2010 65.6 No industry funding	4	415	Mean Difference (IV, Random, 95% CI)	0.05 [-0.11, 0.21]
65.7 Randomised 100+	10	3114	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.11, 0.06]
participants				
65.8 Randomised 250+ participants	5	2442	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.15, 0.08]
66 LDL, mmoL/L - SA fixed-effect	15	3362	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.07, 0.02]
67 LDL, mmoL/L - subgroup by PUFA dose	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
67.1 total PUFA < 1.0% E	3	622	Mean Difference (IV, Random, 95% CI)	0.08 [-0.03, 0.19]
67.2 total PUFA 1.0 to < 2.	5	1790	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.19, 0.09]
0% E			,	
67.3 total PUFA 2.0 to < 5.	3	142	Mean Difference (IV, Random, 95% CI)	0.12 [-0.13, 0.38]
0% E				
67.4 total PUFA 5.0+% E	4	808	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.21, 0.09]
68 LDL, mmoL/L - subgroup by duration	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
68.1 Medium duration 1 to <	9	1085	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.10]
2 years 68.2 Medium-long duration 2	5	1959	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.13, 0.12]
to < 4 years	-		· , , , , , - ,	[=,=]
68.3 Long duration 4+ years	1	318	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.49, 0.28]

69 LDL, mmoL/L - subgroup by primary or secondary prevention	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
69.1 Primary prevention of CVD	11	1915	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.14, 0.07]
69.2 Secondary prevention of CVD	4	1447	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.09]
70 LDL, mmoL/L - subgroup by baseline PUFA dose	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
70.1 Baseline total PUFA < 6% E	3	347	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.30, 0.15]
70.2 Baseline total PUFA 6 to < 11%E	4	1055	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.22, 0.12]
70.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
70.4 Baseline total PUFA unclear	8	1960	Mean Difference (IV, Random, 95% CI)	0.03 [-0.03, 0.10]
71 LDL, mmoL/L - subgroup by replacement	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
71.1 PUFA replaced saturated fats	2	222	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.21, 0.14]
71.2 PUFA replaced monounsaturated fats	6	1776	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.12, 0.12]
71.3 PUFA replaced carbohydrates	6	1106	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.18, 0.06]
71.4 PUFA replaced protein	3	682	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.26, 0.10]
71.5 PUFA replaced unclear	2	409	Mean Difference (IV, Random, 95% CI)	0.10 [-0.03, 0.23]
72 LDL, mmoL/L - subgroup by sex	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
72.1 > 70% men	7	1972	Mean Difference (IV, Random, 95% CI)	0.04 [-0.03, 0.10]
72.2 > 70% women	2	251	Mean Difference (IV, Random, 95% CI)	0.02 [-0.46, 0.49]
72.3 men & women	5	1107	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.21, 0.06]
72.4 sex not reported	1	32	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.59, 0.39]
73 LDL, mmoL/L - subgroup by	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
age			, , , , , , , , , , , , , , , , , , , ,	
73.1 Mean age < 50 years	2	101	Mean Difference (IV, Random, 95% CI)	0.25 [-0.11, 0.61]
73.2 Mean age 50 to < 65	8	1177	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.10]
years				
73.3 Mean age 65+ years	3	1956	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.23, 0.07]
73.4 Mean age unclear	2	128	Mean Difference (IV, Random, 95% CI)	0.05 [-0.26, 0.36]
74 LDL, mmoL/L - subgroup by statin use	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
74.1 < 50% on statins	8	1197	Mean Difference (IV, Random, 95% CI)	0.00 [-0.13, 0.13]
74.2 50+% on statins	5	1515	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.08]
74.3 Percentage on statins unclear	2	650	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.33, 0.25]
75 LDL, mmoL/L - subgroup by intervention type	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
75.1 Dietary advice	2	208	Mean Difference (IV, Random, 95% CI)	0.22 [-0.05, 0.48]
75.2 Supplemental foods &	5	2178	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.18, 0.05]
diet provided	_	-1,0	(-,, 2, , , , , , , , , , , , , , ,	5.57 [5.20, 5.65]

75.3 Supplements (capsules &	7	922	Mean Difference (IV, Random, 95% CI)	0.02 [-0.09, 0.13]
unusual foods)				
75.4 Any combination	1	54	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.51, 0.37]

Comparison 4. Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SYSTOLIC BLOOD	10	7356	Mean Difference (IV, Random, 95% CI)	-0.47 [-2.20, 1.26]
PRESSURE (sBP, mmHg)				
2 DIASTOLIC BLOOD	9	7327	Mean Difference (IV, Random, 95% CI)	0.24 [-0.55, 1.02]
PRESSURE (dBP, mmHg)				
3 SERIOUS ADVERSE EVENTS	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
(SAEs)				
3.1 Pulmonary embolism	2	2087	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.48, 9.57]
3.2 Multiple Sclerosis	2	268	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.95, 1.30]
worsened or had acute attack -				
GLA supplement				
3.3 Bleeding	2	748	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.34, 1.85]
3.4 GI hospitalisation	1	200	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.53, 5.79]
3.5 Retinopathy	1	2424	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.56, 1.86]
4 DROPOUTS	27	8574	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.13]

Analysis I.I. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome I ALL-CAUSE MORTALITY.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

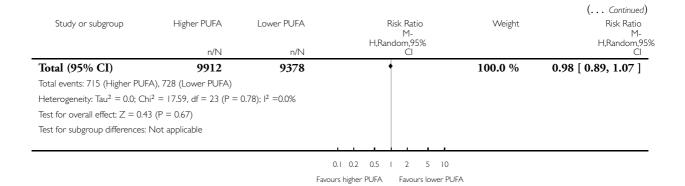
Outcome: I ALL-CAUSE MORTALITY

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
AlphaOmega - ALA	182/2409	188/2428	+	22.3 %	0.98 [0.80, 1.19]
Bates 1978	0/58	2/58	-	0.1 %	0.20 [0.01, 4.08]
Bates 1989	1/155	0/157		0.1 %	3.04 [0.12, 74.02]
Black 1994	2/67	1/66		0.2 %	1.97 [0.18, 21.21]
Brox 2001	0/80	1/40		0.1 %	0.17 [0.01, 4.05]
DART fat 1989	111/1018	113/1015	+	14.0 %	0.98 [0.76, 1.25]
DIPP-Tokudome 2015	2/104	3/101		0.3 %	0.65 [0.11, 3.79]
Doi 2014	2/119	9/119	 	0.4 %	0.22 [0.05, 1.01]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [0.12, 71.97]
EPIC-2 2008	0/189	1/190	-	0.1 %	0.34 [0.01, 8.17]
FAAT - Leaf 2005	13/200	12/202		1.5 %	1.09 [0.51, 2.34]
HARP- Sacks 1995	0/41	1/39	•	0.1 %	0.32 [0.01, 7.57]
Kumar 2013	1/39	1/39		0.1 %	1.00 [0.06, 15.43]
Ley 2004	2/70	1/66		0.2 %	1.89 [0.18, 20.31]
McIllmurray 1987	10/25	12/24		2.2 %	0.80 [0.43, 1.49]
MRC 1968	28/199	31/194	-	3.9 %	0.88 [0.55, 1.41]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [0.17, 56.84]
PREDIMED 2013	116/2454	118/2543	+	13.7 %	1.02 [0.79, 1.31]
Raitt 2005	4/100	10/100		0.7 %	0.40 [0.13, 1.23]
Rose 1965	5/28	3/26		0.5 %	1.55 [0.41, 5.84]
Sydney Diet-Heart 1978	38/221	27/237	-	4.1 %	1.51 [0.95, 2.39]
Veterans Admin 1969	174/424	177/422	+	33.5 %	0.98 [0.83, 1.15]
Vijayakumar 2014	0/100	2/100	-	0.1 %	0.20 [0.01, 4.11]
WINS 2006	19/1462	15/975		1.9 %	0.84 [0.43, 1.65]

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

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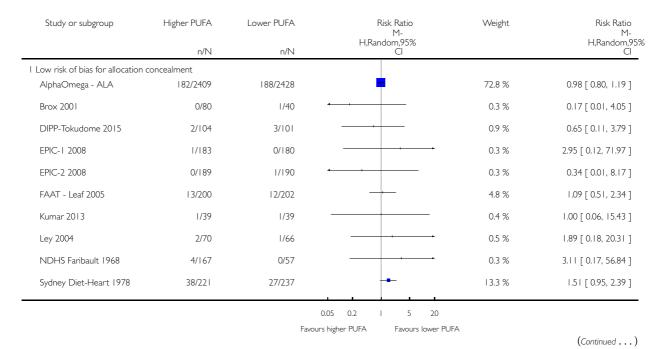


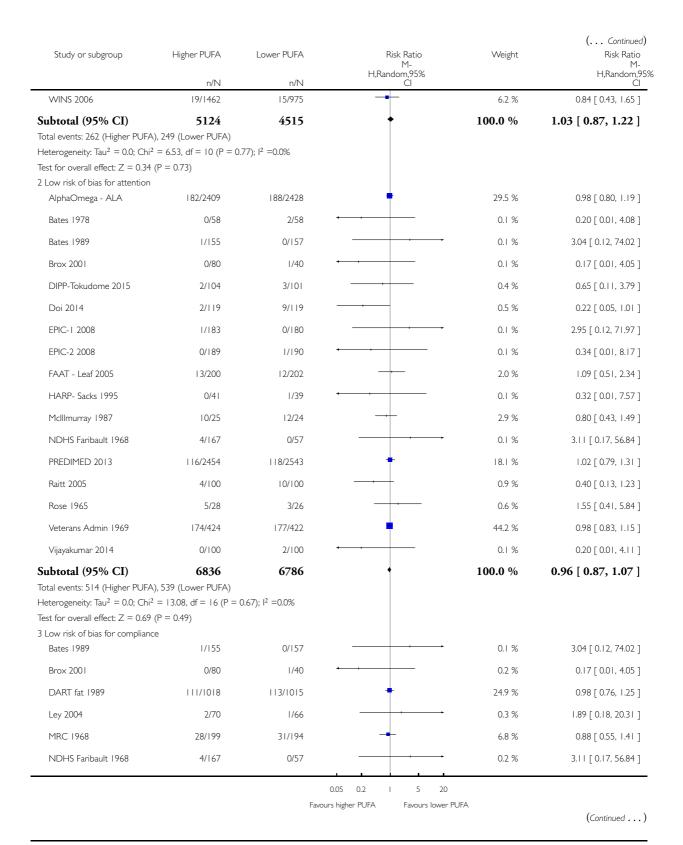
Analysis 1.2. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 2 All-cause mortality - SA.

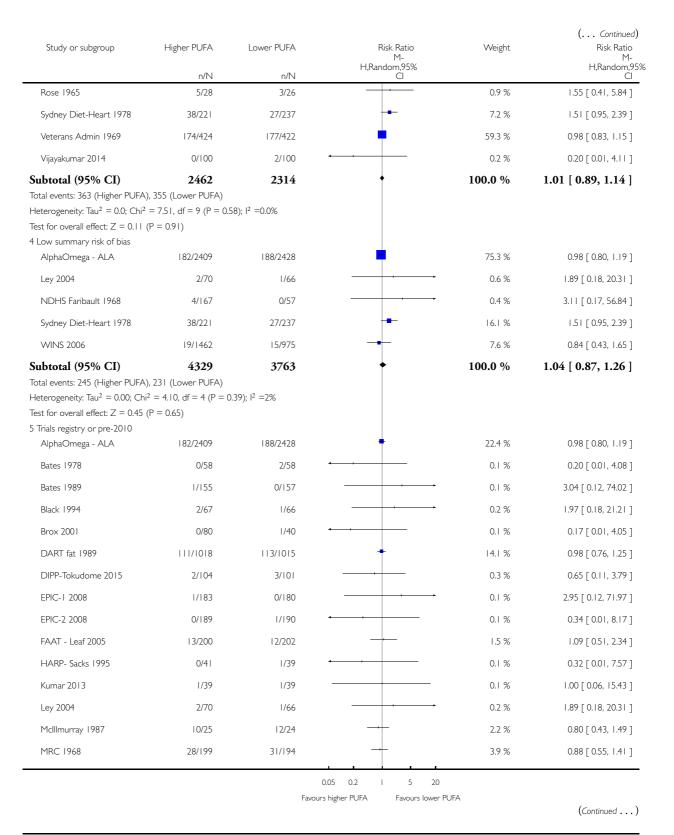
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

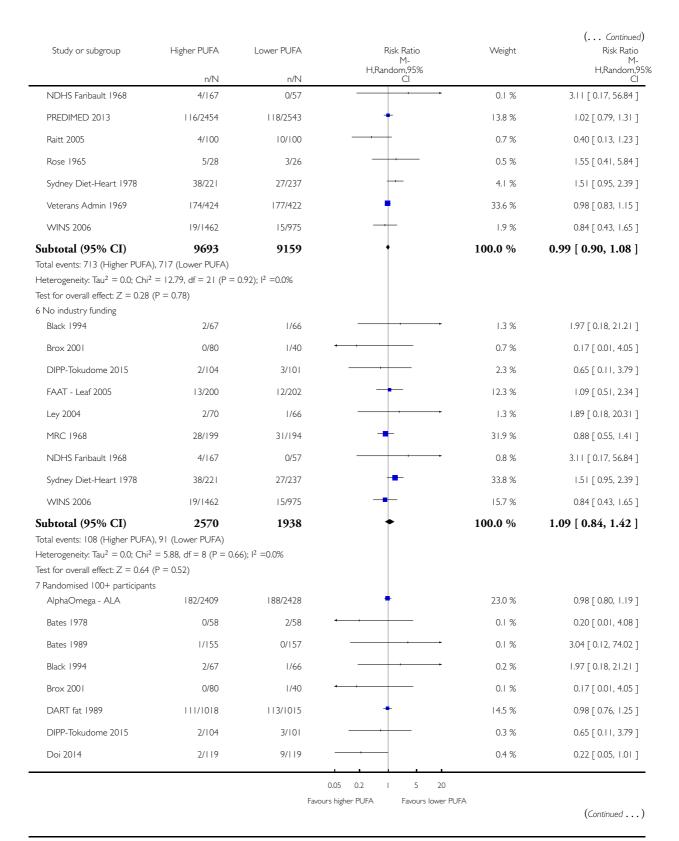
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

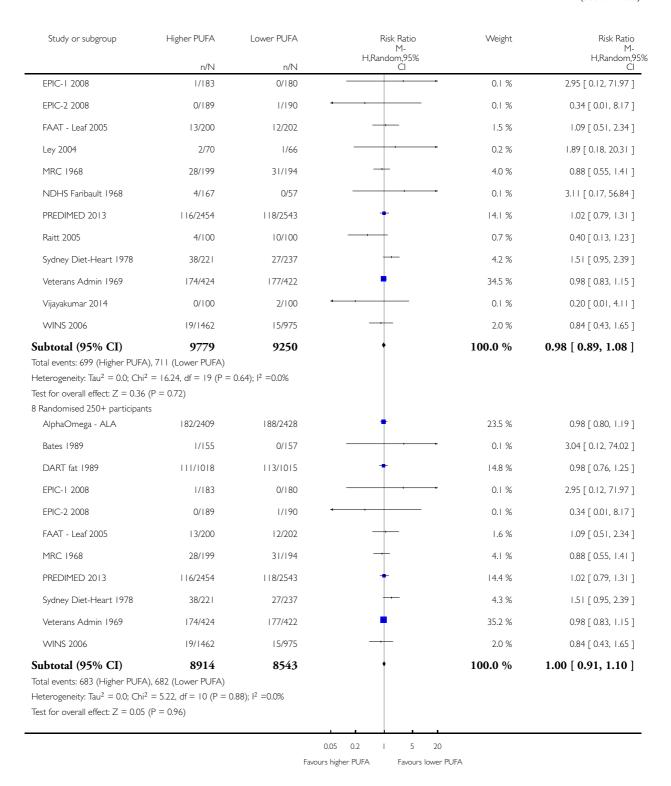
Outcome: 2 All-cause mortality - SA











Analysis I.3. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 3 All-cause mortality - SA fixed-effect.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

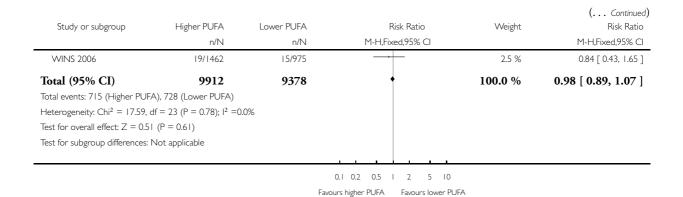
Outcome: 3 All-cause mortality - SA fixed-effect

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% Cl
AlphaOmega - ALA	182/2409	188/2428	+	25.5 %	0.98 [0.80, 1.19]
Bates 1978	0/58	2/58		0.3 %	0.20 [0.01, 4.08]
Bates 1989	1/155	0/157		0.1 %	3.04 [0.12, 74.02]
Black 1994	2/67	1/66	-	0.1 %	1.97 [0.18, 21.21]
Brox 2001	0/80	1/40		0.3 %	0.17 [0.01, 4.05]
DART fat 1989	111/1018	113/1015	+	15.4 %	0.98 [0.76, 1.25]
DIPP-Tokudome 2015	2/104	3/101		0.4 %	0.65 [0.11, 3.79]
Doi 2014	2/119	9/119	-	1.2 %	0.22 [0.05, 1.01]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [0.12, 71.97]
EPIC-2 2008	0/189	1/190	-	0.2 %	0.34 [0.01, 8.17]
FAAT - Leaf 2005	13/200	12/202		1.6 %	1.09 [0.51, 2.34]
HARP- Sacks 1995	0/41	1/39	•	0.2 %	0.32 [0.01, 7.57]
Kumar 2013	1/39	1/39	-	0.1 %	1.00 [0.06, 15.43]
Ley 2004	2/70	1/66	-	0.1 %	1.89 [0.18, 20.31]
McIllmurray 1987	10/25	12/24		1.7 %	0.80 [0.43, 1.49]
MRC 1968	28/199	31/194	-	4.3 %	0.88 [0.55, 1.41]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [0.17, 56.84]
PREDIMED 2013	116/2454	118/2543	+	15.8 %	1.02 [0.79, 1.31]
Raitt 2005	4/100	10/100		1.4 %	0.40 [0.13, 1.23]
Rose 1965	5/28	3/26		0.4 %	1.55 [0.41, 5.84]
Sydney Diet-Heart 1978	38/221	27/237		3.6 %	1.51 [0.95, 2.39]
Veterans Admin 1969	174/424	177/422	+	24.2 %	0.98 [0.83, 1.15]
Vijayakumar 2014	0/100	2/100		0.3 %	0.20 [0.01, 4.11]

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

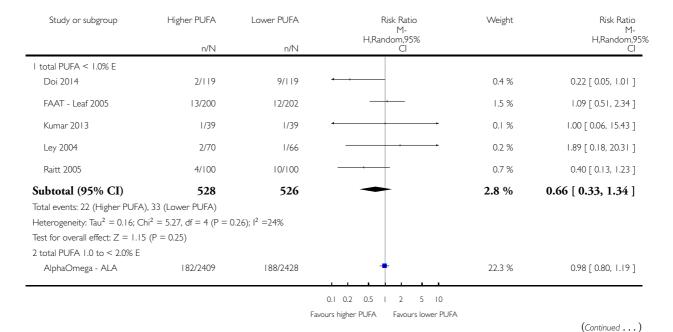
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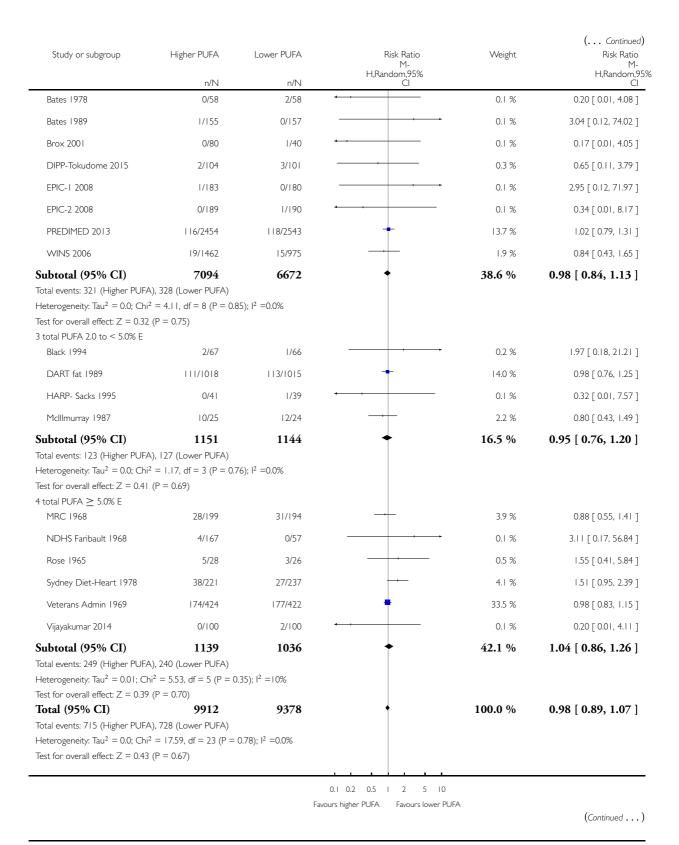


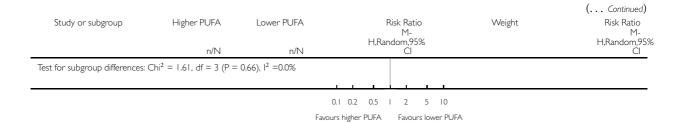
Analysis 1.4. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 4 All-cause mortality - subgroup by PUFA dose.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 4 All-cause mortality - subgroup by PUFA dose



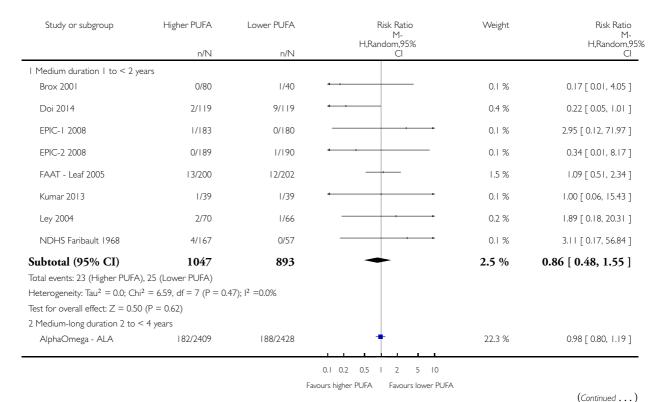


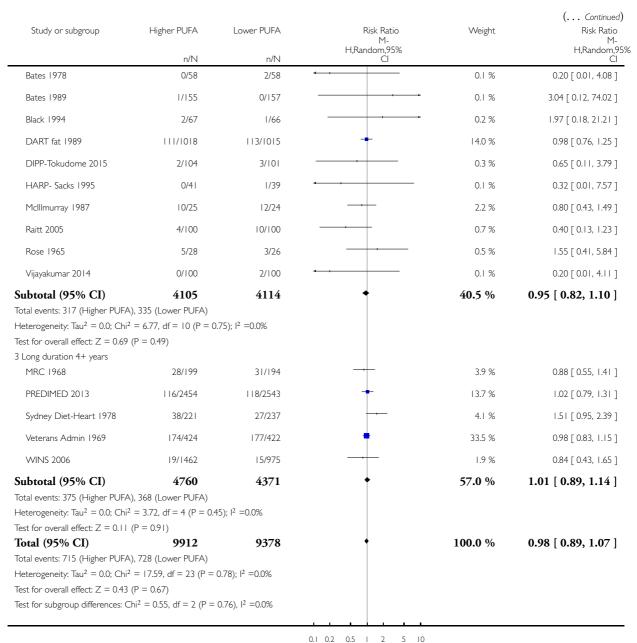


Analysis I.5. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 5 All-cause mortality - subgroup by duration.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 5 All-cause mortality - subgroup by duration



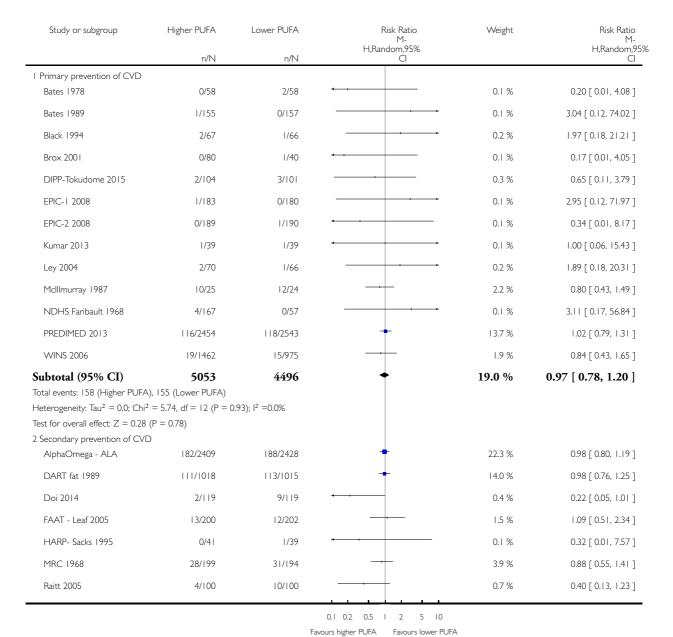


Favours higher PUFA Favours lower PUFA

Analysis I.6. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 6 All-cause mortality - subgroup by primary or secondary prevention.

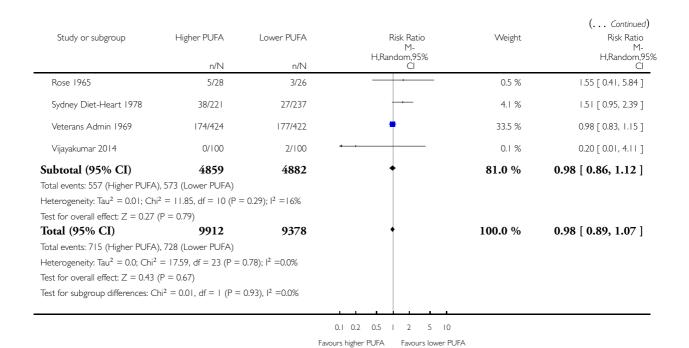
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 6 All-cause mortality - subgroup by primary or secondary prevention



Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease (Review) Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

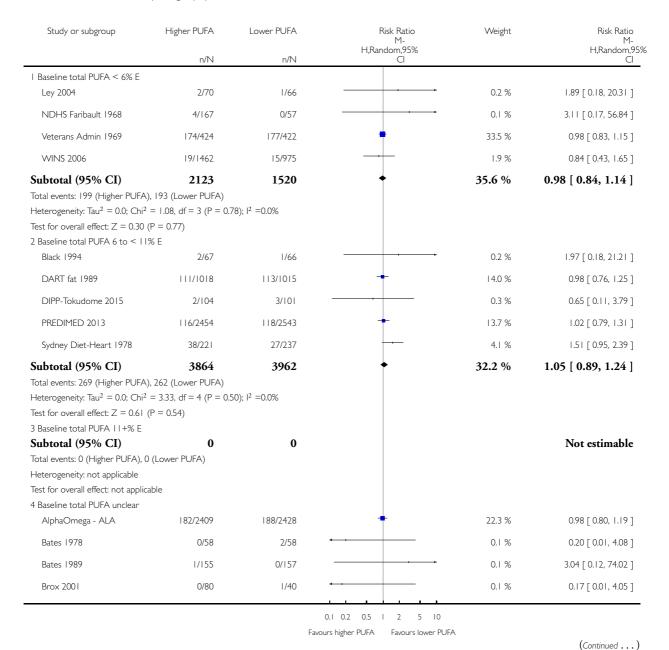
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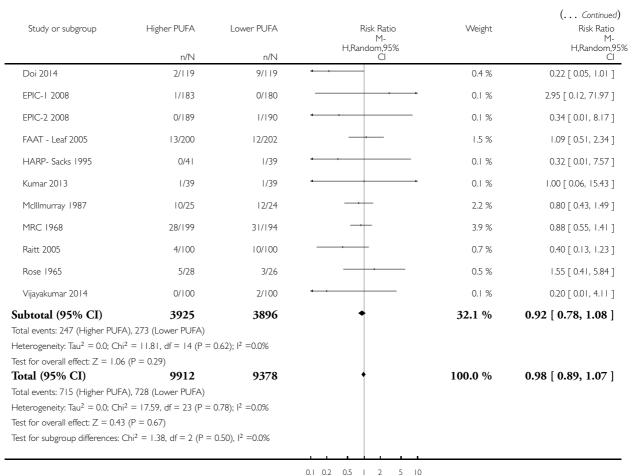


Analysis I.7. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 7 All-cause mortality - subgroup by baseline PUFA dose.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 7 All-cause mortality - subgroup by baseline PUFA dose



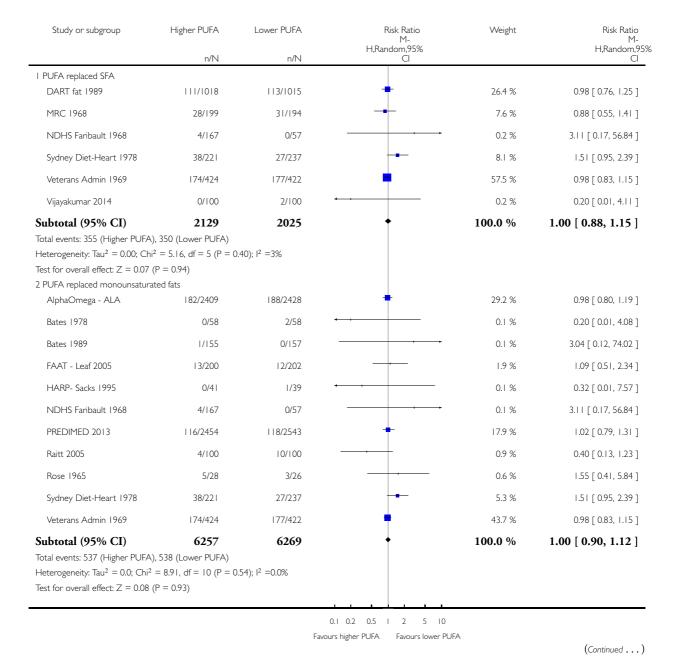


Favours higher PUFA Favours lower PUFA

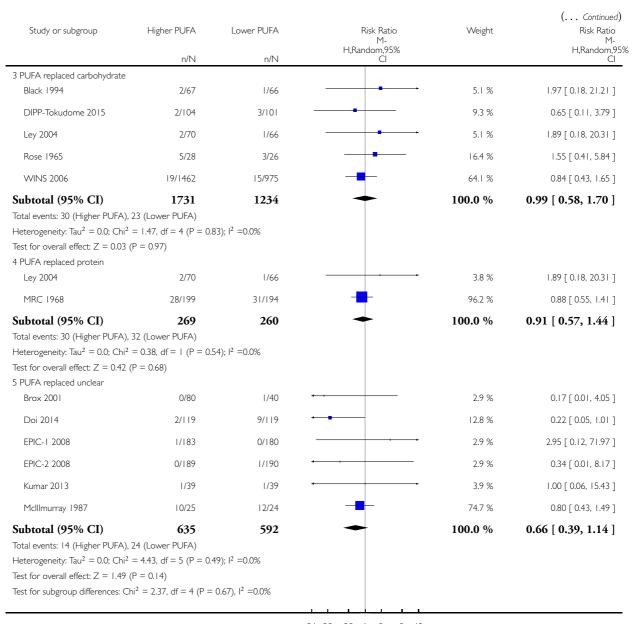
Analysis I.8. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 8 All-cause mortality - subgroup by replacement.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 8 All-cause mortality - subgroup by replacement



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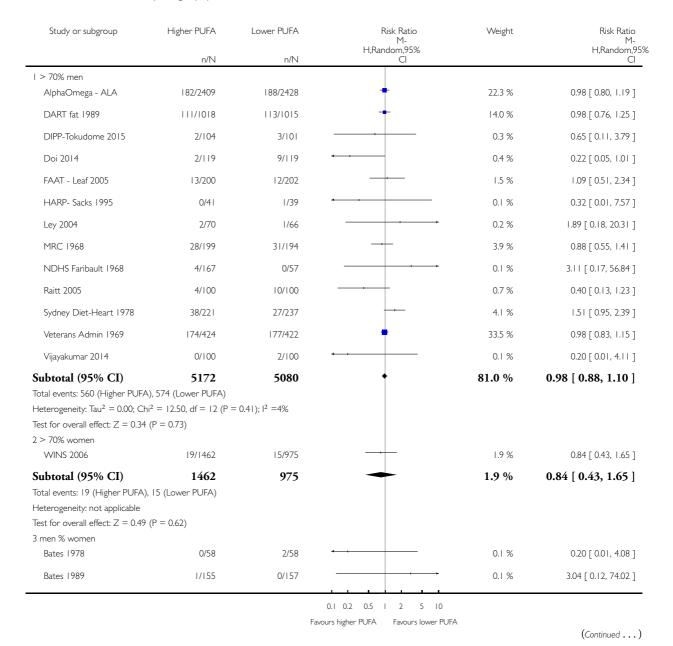
0.1 0.2 0.5 1 2 5 10

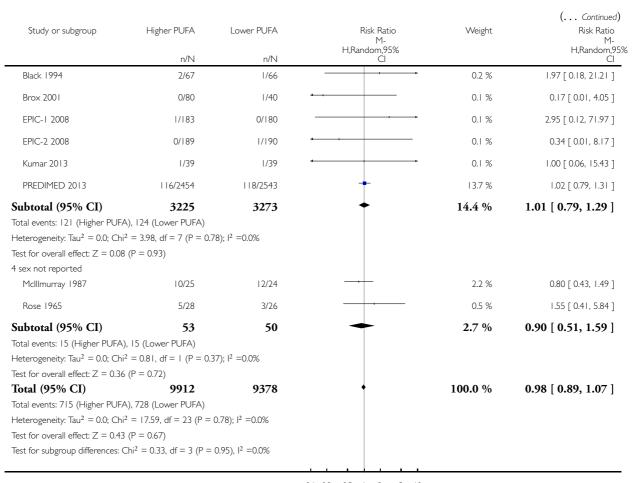
Favours higher PUFA Favours lower PUFA

Analysis I.9. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 9 All-cause mortality - subgroup by sex.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 9 All-cause mortality - subgroup by sex





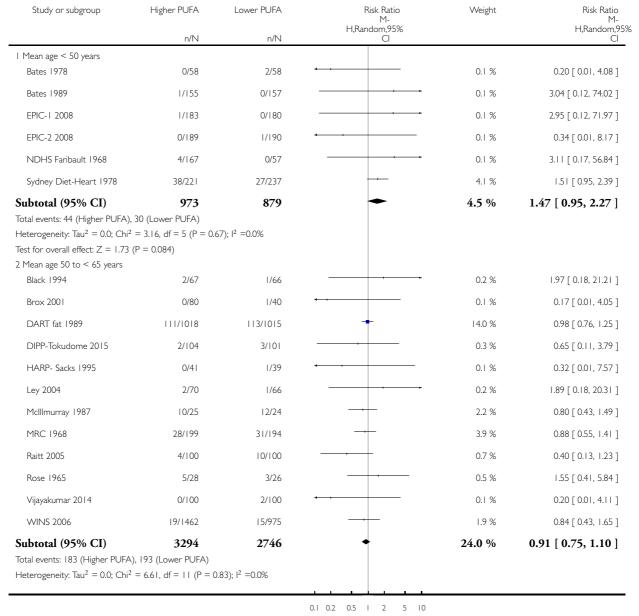
0.1 0.2 0.5 I 2 5 I0

Favours higher PUFA Favours lower PUFA

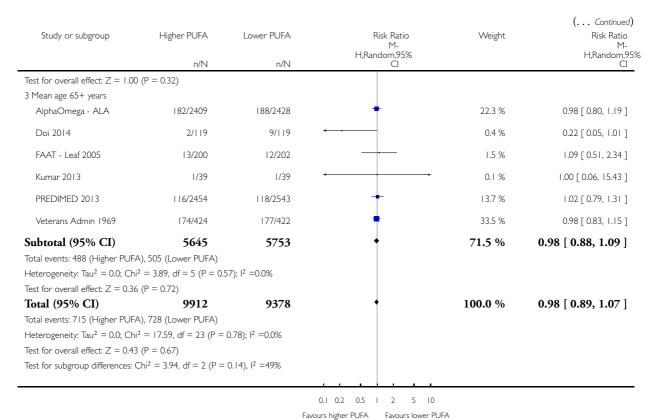
Analysis 1.10. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 10 All-cause mortality - subgroup by age.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 10 All-cause mortality - subgroup by age



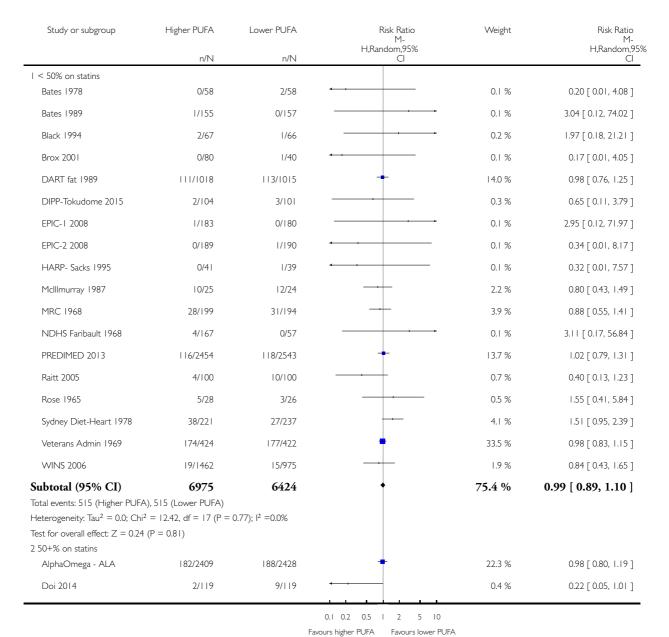
Favours higher PUFA Favours lower PUFA (Continued . . .)



Analysis I.II. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome II All-cause mortality - subgroup by statin use.

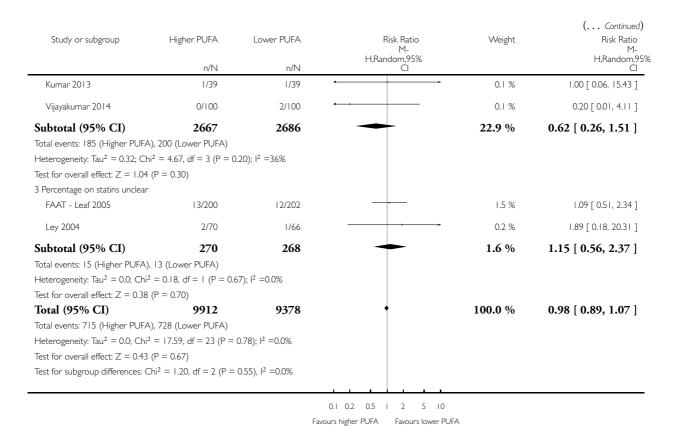
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: II All-cause mortality - subgroup by statin use



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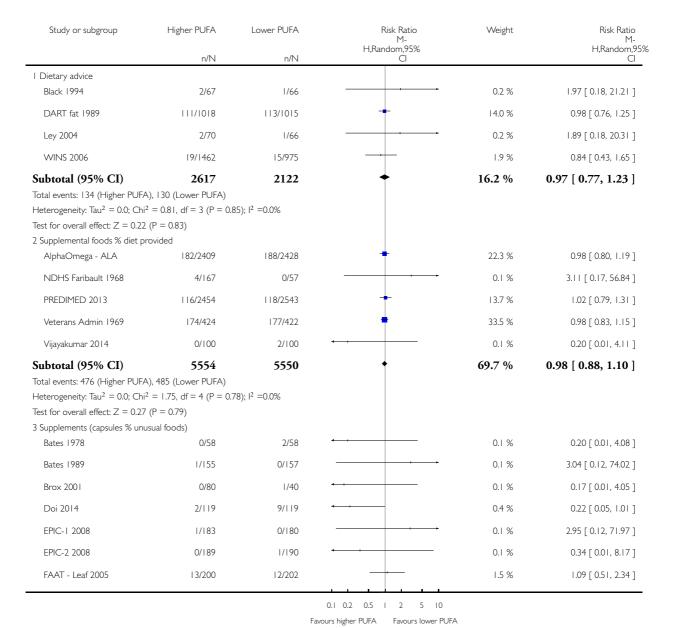
(Continued ...)



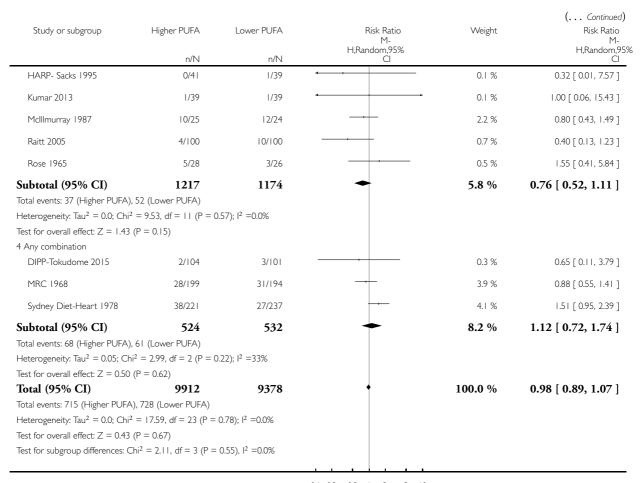
Analysis 1.12. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 12 All-cause mortality - subgroup by intervention type.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 12 All-cause mortality - subgroup by intervention type



(Continued . . .)



0.1 0.2 0.5 1 2 5 10

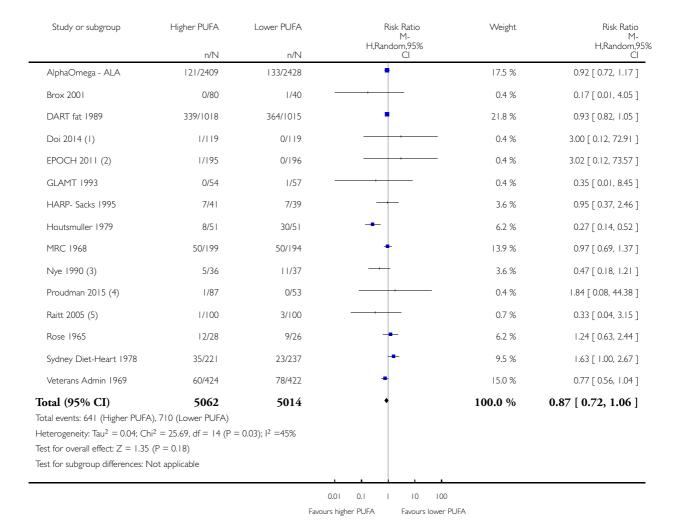
Favours higher PUFA Favours lower PUFA

Analysis 1.13. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 13 CORONARY HEART DISEASE (CHD) EVENTS: myocardial infarction (fatal or non-fatal) or angina.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 13 CORONARY HEART DISEASE (CHD) EVENTS: myocardial infarction (fatal or non-fatal) or angina



(I) Total MI

(2) Total MI

(3) Angina

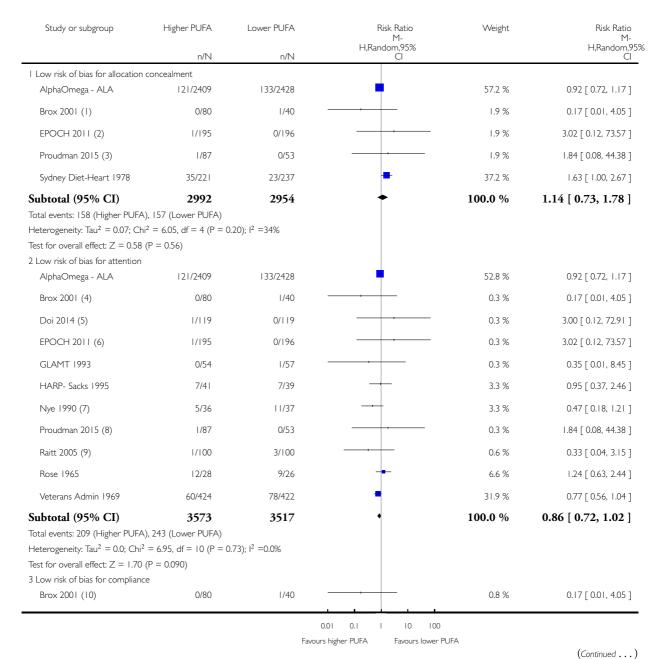
(4) Total MI

(5) Total MI

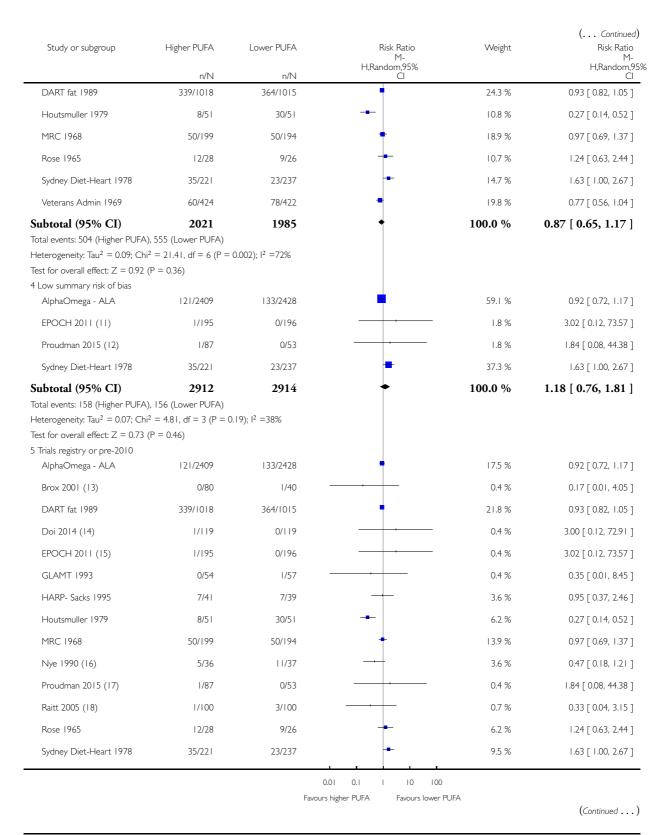
Analysis 1.14. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 14 CHD events - SA.

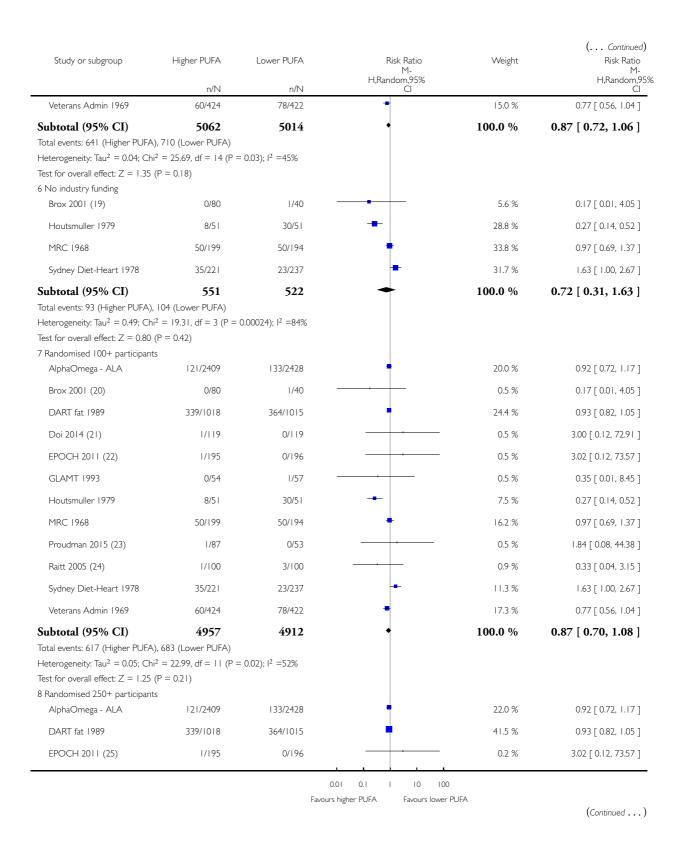
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

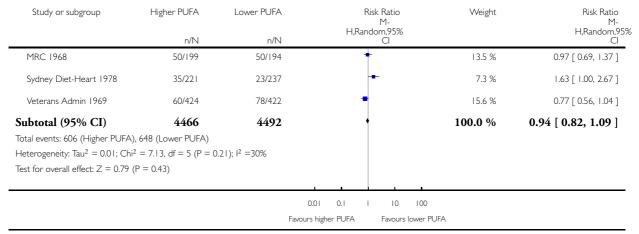
Outcome: 14 CHD events - SA



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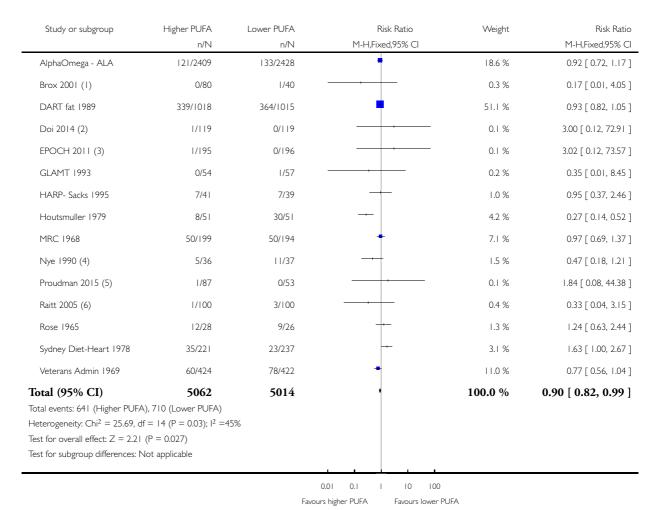
- (I) Total MI
- (2) Total MI
- (3) Total MI
- (4) Total MI
- (5) Total MI
- (6) Total MI
- (7) Angina
- (8) Total MI
- (9) Total MI
- (10) Total MI
- (11) Total MI
- (12) Total MI
- (13) Total MI
- (14) Total MI
- (15) Total MI
- (16) Angina
- (17) Total MI
- (18) Total MI
- (19) Total MI
- (20) Total MI
- (21) Total MI
- (22) Total MI
- (23) Total MI
- (24) Total MI
- (25) Total MI

Analysis 1.15. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 15 CHD events - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 15 CHD events - SA fixed-effect



(I) Total MI

(2) Total MI

(3) Total MI

(4) Angina

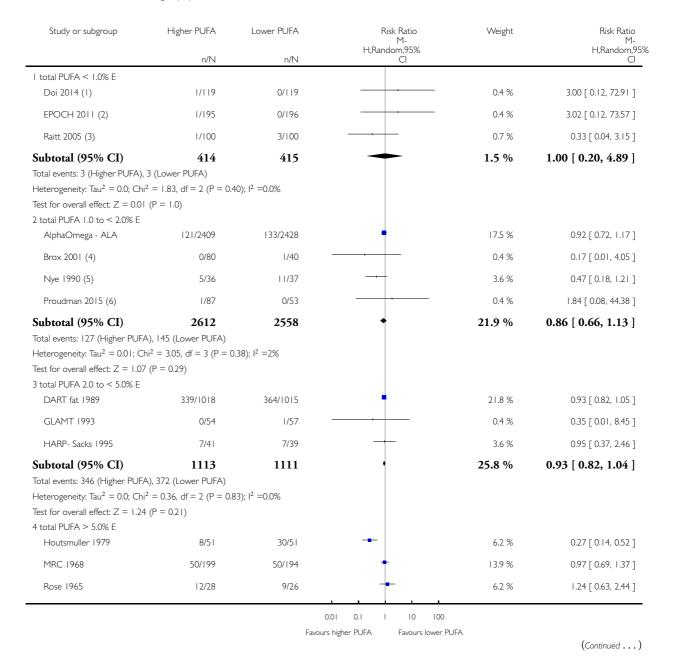
(5) Total MI

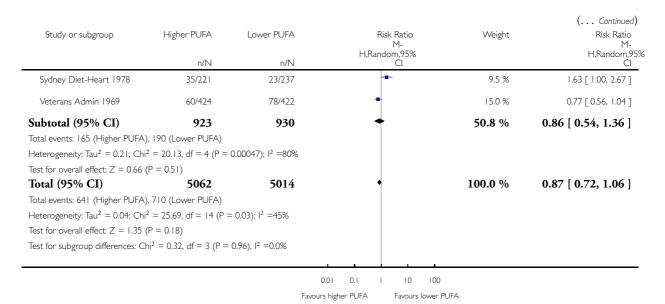
(6) Total MI

Analysis 1.16. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 16 CHD events - subgroup by PUFA dose.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 16 CHD events - subgroup by PUFA dose



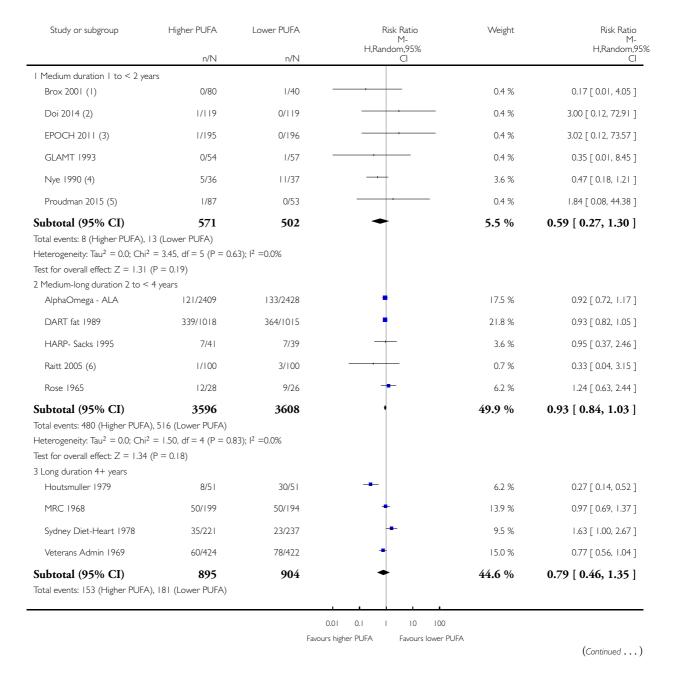


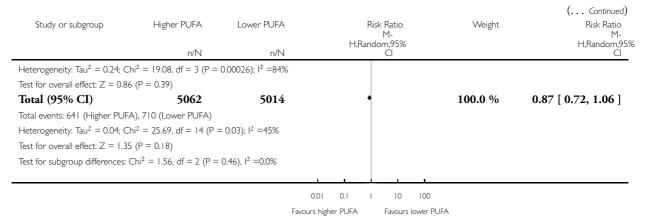
- (I) Total MI
- (2) Total MI
- (3) Total MI
- (4) Total MI
- (5) Angina
- (6) Total MI

Analysis 1.17. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 17 CHD events - subgroup by duration.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 17 CHD events - subgroup by duration





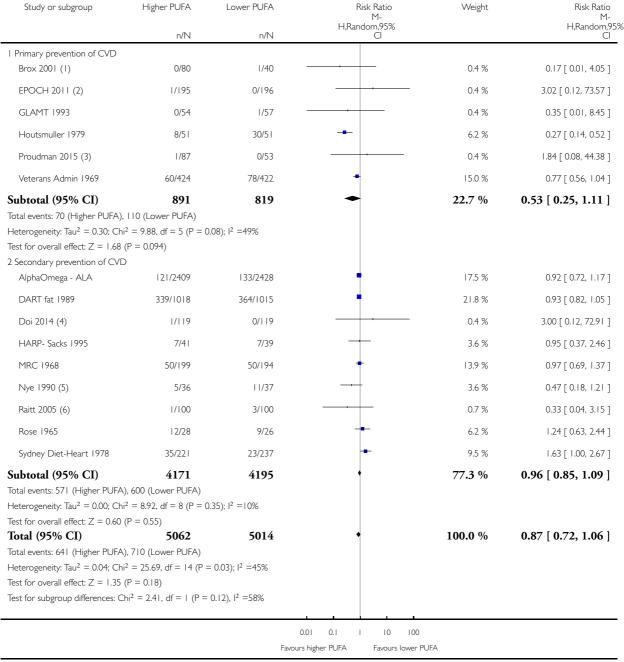
- (I) Total MI
- (2) Total MI
- (3) Total MI
- (4) Angina
- (5) Total MI
- (6) Total MI

Analysis 1.18. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 18 CHD events - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 18 CHD events - subgroup by primary or secondary prevention

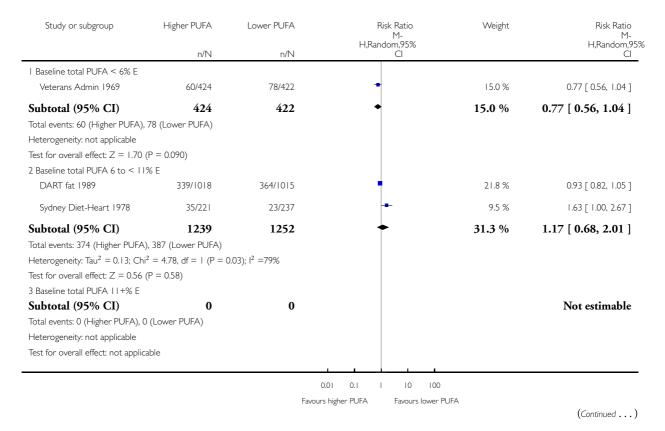


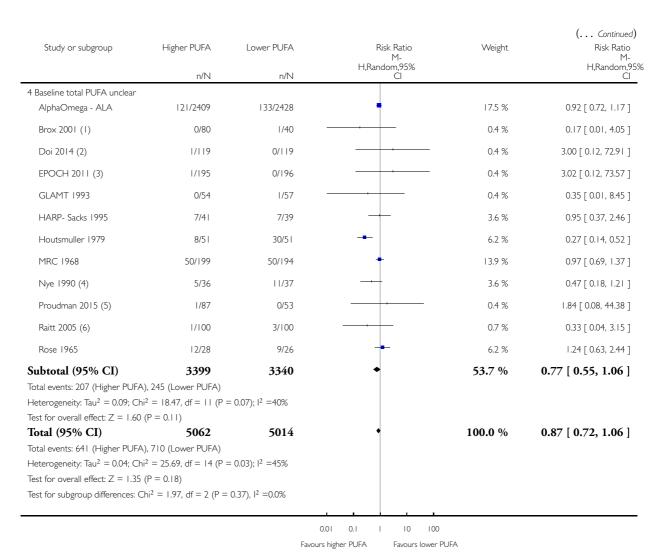
- (I) Total MI
- (2) Total MI
- (3) Total MI
- (4) Total MI
- (5) Angina
- (6) Total MI

Analysis 1.19. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 19 CHD events - subgroup by baseline PUFA dose.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 19 CHD events - subgroup by baseline PUFA dose



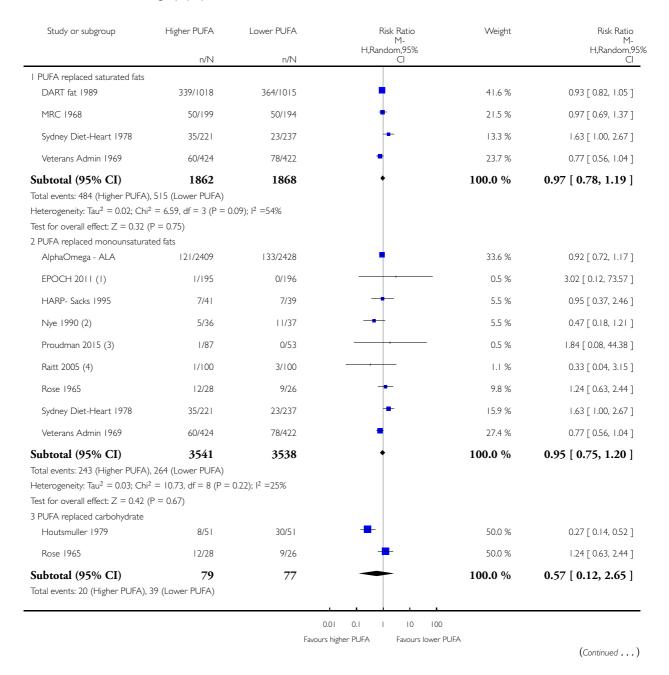


- (I) Total MI
- (2) Total MI
- (3) Total MI
- (4) Angina
- (5) Total MI
- (6) Total MI

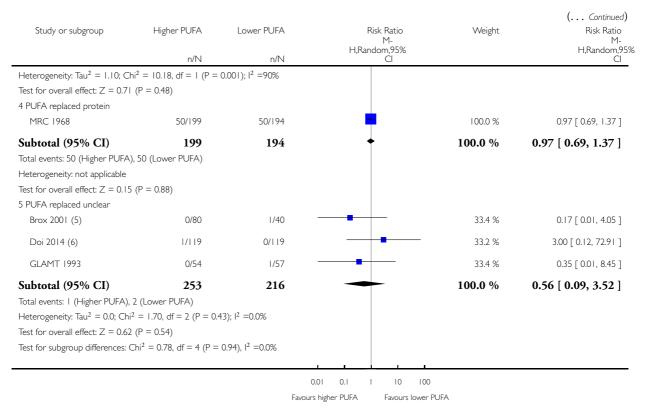
Analysis 1.20. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 20 CHD events - subgroup by replacement.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 20 CHD events - subgroup by replacement



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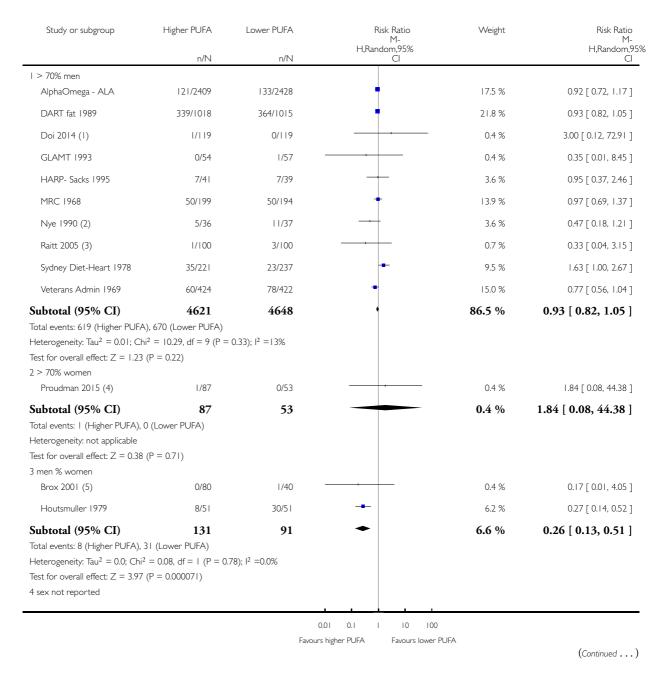


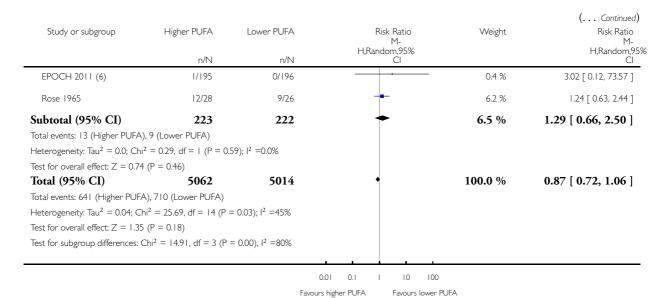
- (I) Total MI
- (2) Angina
- (3) Total MI
- (4) Total MI
- (5) Total MI
- (6) Total MI

Analysis 1.21. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 21 CHD events - subgroup by sex.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 21 CHD events - subgroup by sex



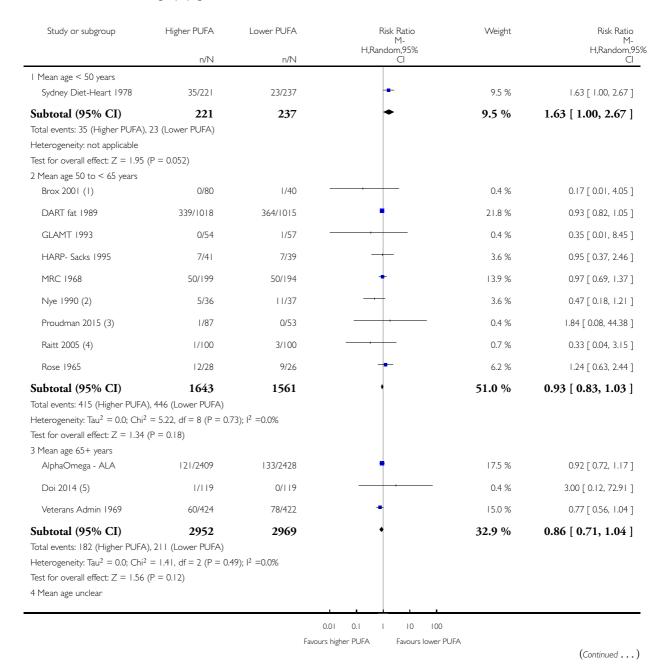


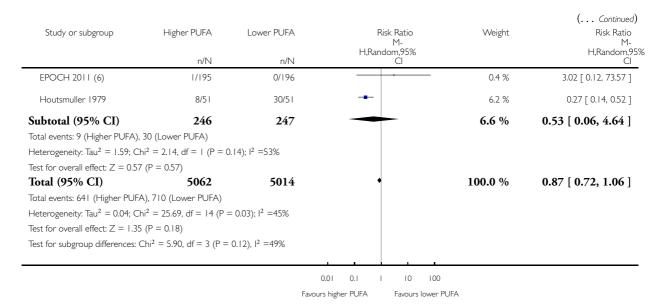
- (I) Total MI
- (2) Angina
- (3) Total MI
- (4) Total MI
- (5) Total MI
- (6) Total MI

Analysis 1.22. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 22 CHD events - subgroup by age.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 22 CHD events - subgroup by age





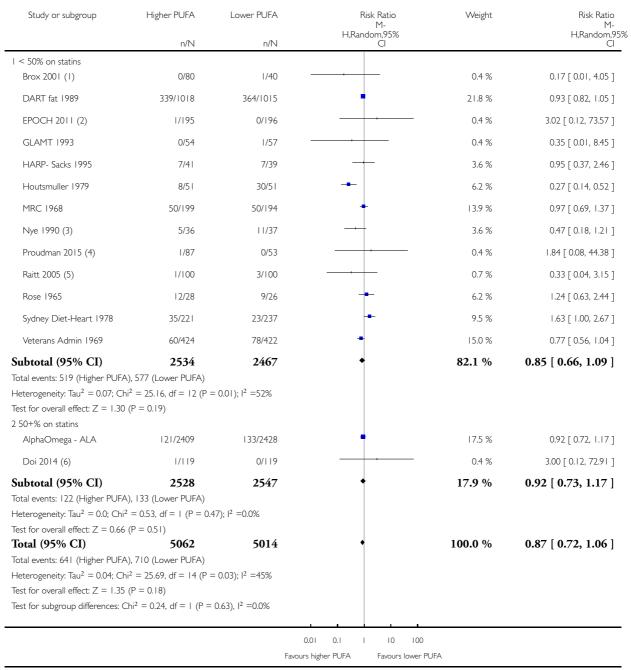
- (I) Total MI
- (2) Angina
- (3) Total MI
- (4) Total MI
- (5) Total MI
- (6) Total MI

Analysis 1.23. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 23 CHD events - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 23 CHD events - subgroup by statin use

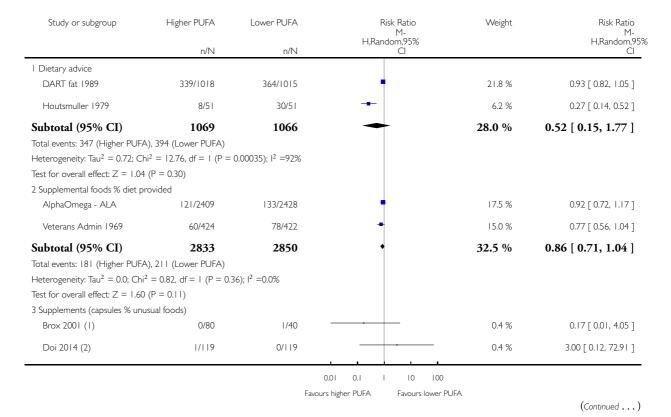


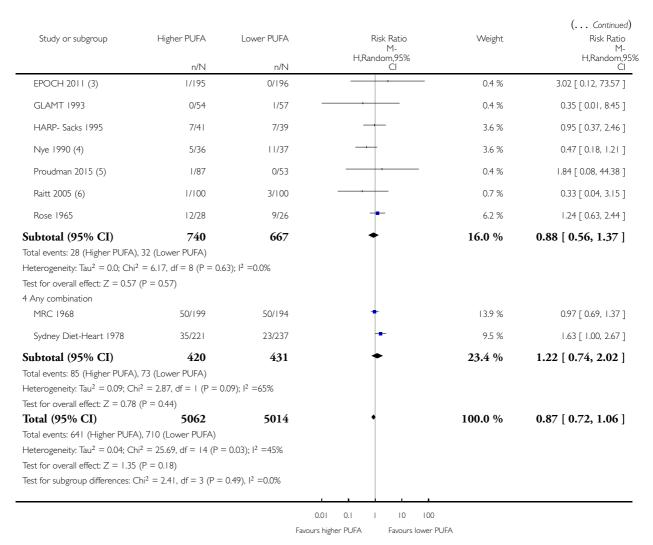
- (I) Total MI
- (2) Total MI
- (3) Angina
- (4) Total MI
- (5) Total MI
- (6) Total MI

Analysis 1.24. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 24 CHD events - subgroup by intervention type.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 24 CHD events - subgroup by intervention type





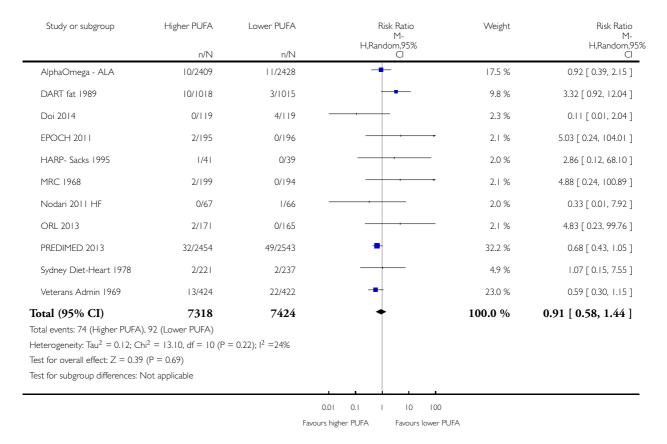
- (I) Total MI
- (2) Total MI
- (3) Total MI
- (4) Angina
- (5) Total MI
- (6) Total MI

Analysis 1.25. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 25 STROKE - fatal & non fatal.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

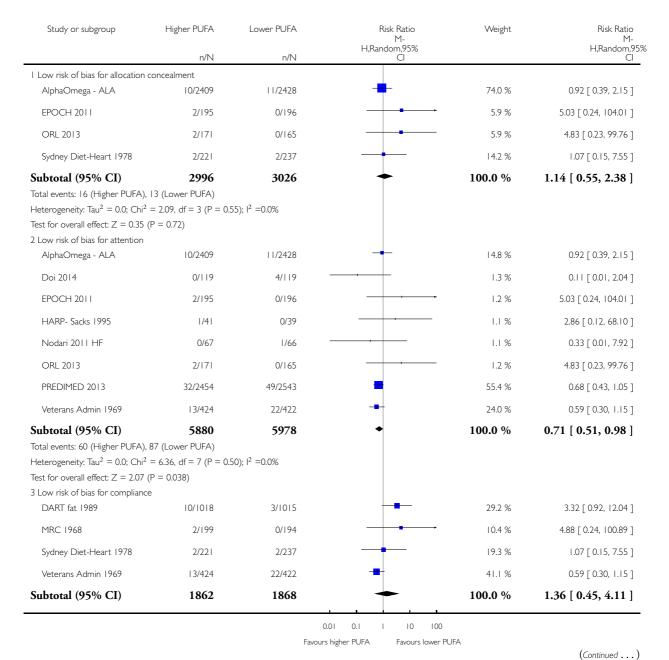
Outcome: 25 STROKE - fatal % non fatal



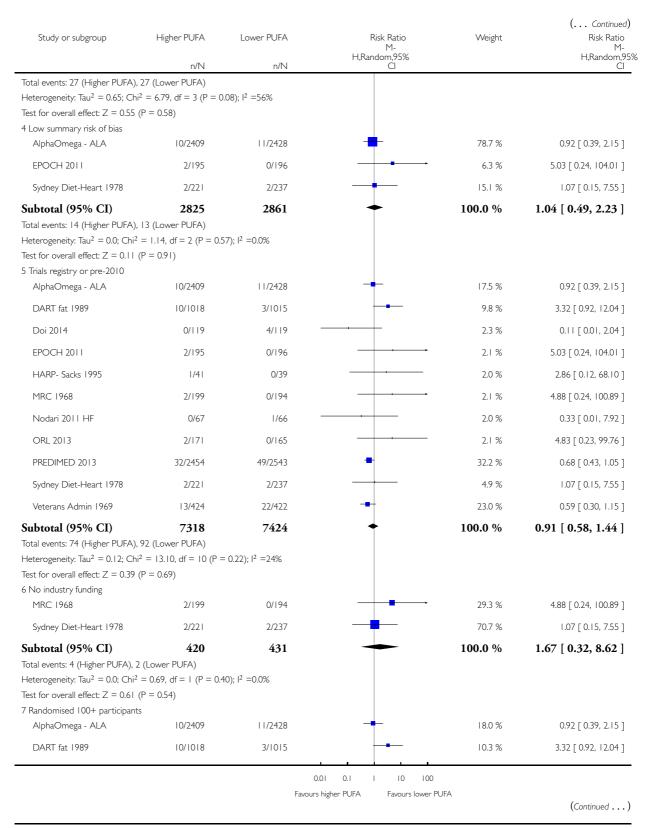
Analysis 1.26. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 26 Stroke - SA.

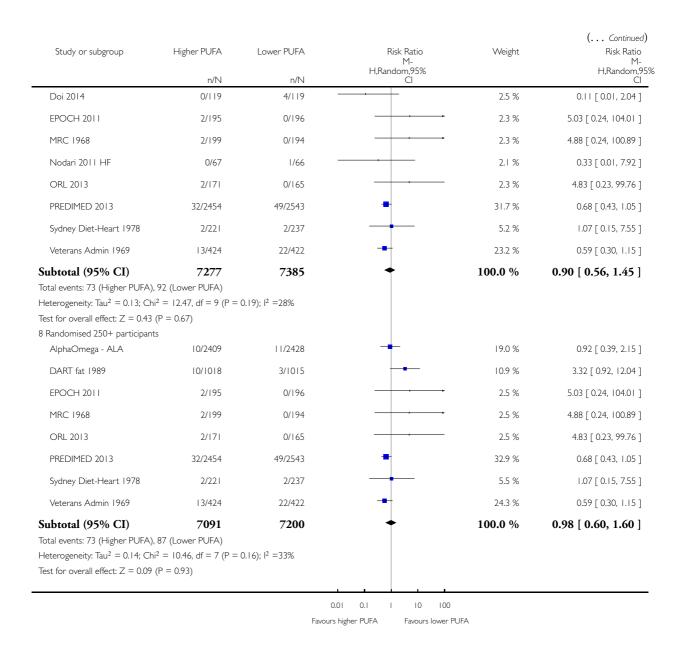
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 26 Stroke - SA



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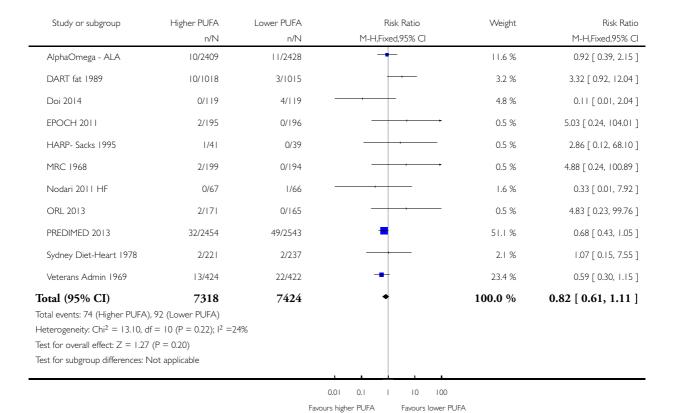


Analysis 1.27. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 27 Stroke - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

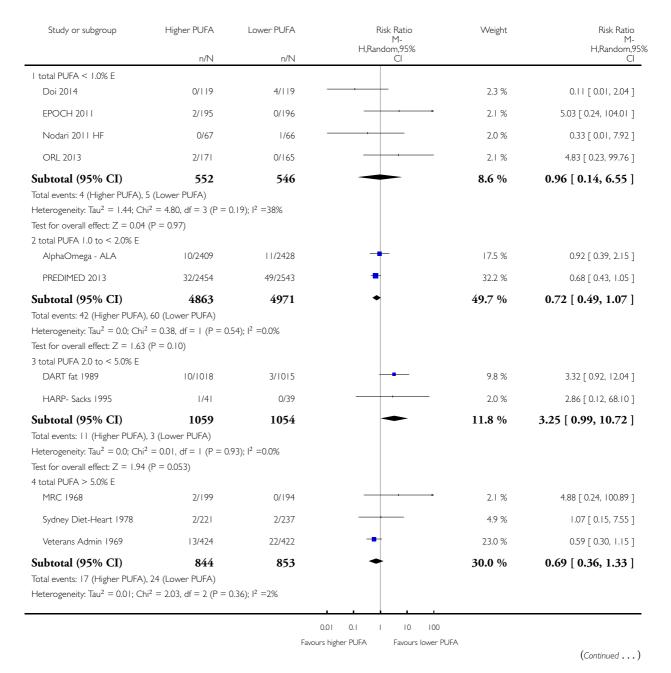
Outcome: 27 Stroke - SA fixed-effect

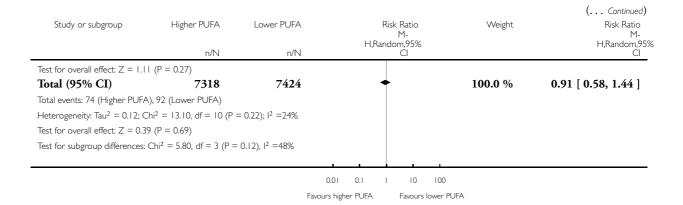


Analysis 1.28. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 28 Stroke - subgroup by PUFA dose.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 28 Stroke - subgroup by PUFA dose



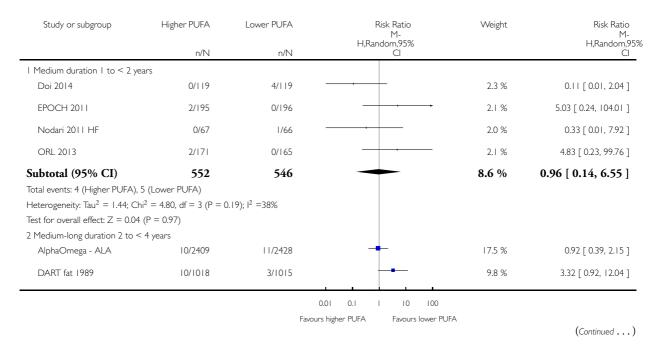


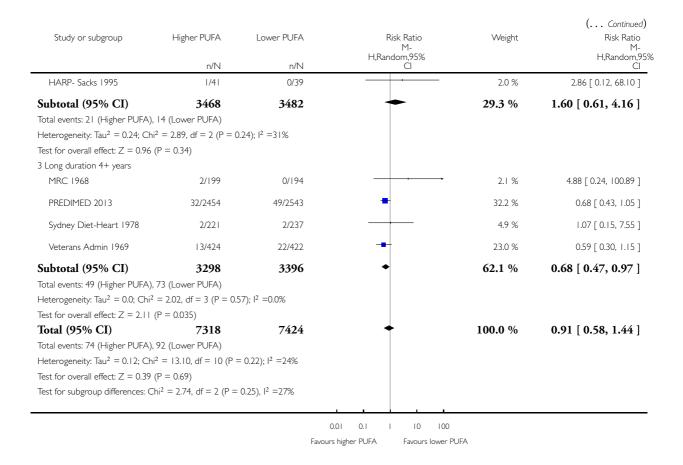
Analysis 1.29. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 29 Stroke - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 29 Stroke - subgroup by duration

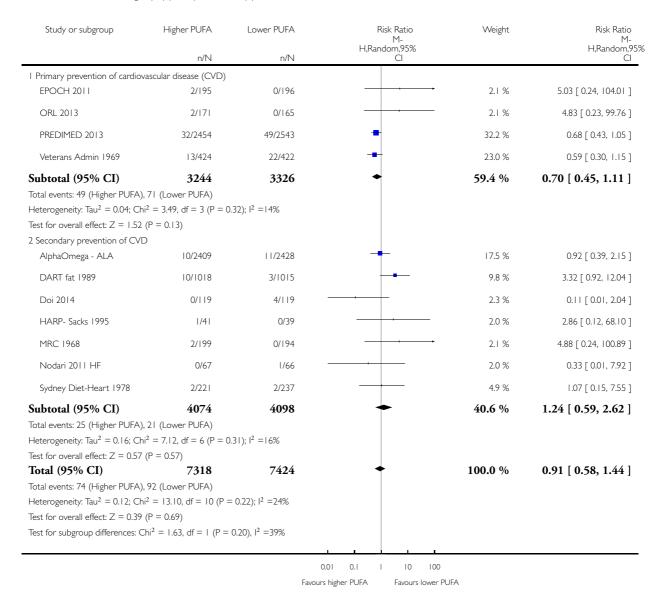




Analysis 1.30. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 30 Stroke - subgroup by primary or secondary prevention.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

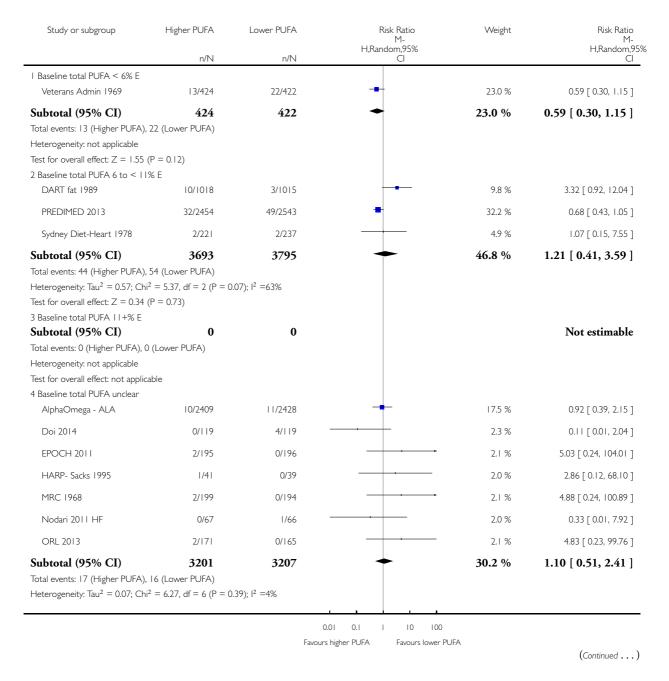
Outcome: 30 Stroke - subgroup by primary or secondary prevention

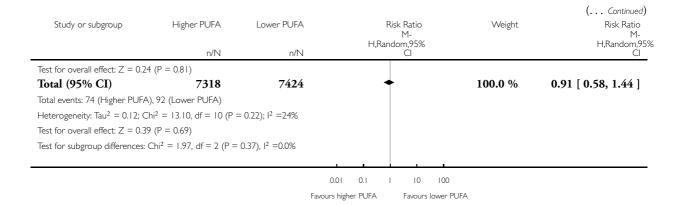


Analysis 1.31. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 31 Stroke - subgroup by baseline PUFA dose.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 31 Stroke - subgroup by baseline PUFA dose



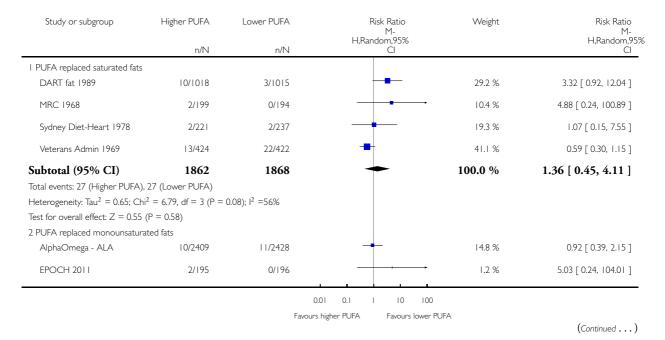


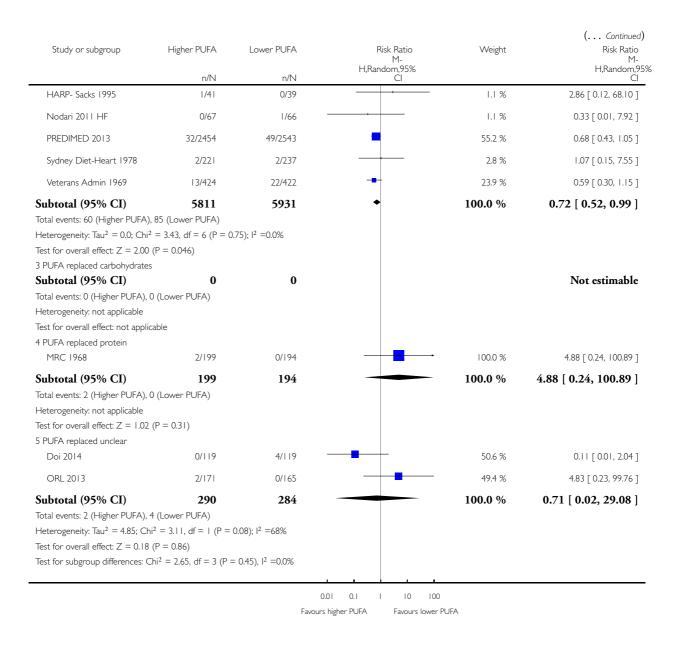
Analysis 1.32. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 32 Stroke - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 32 Stroke - subgroup by replacement

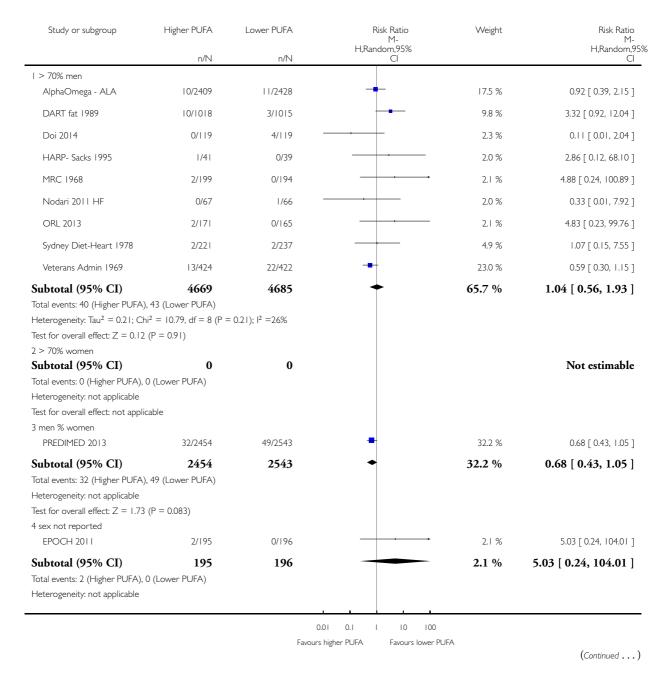


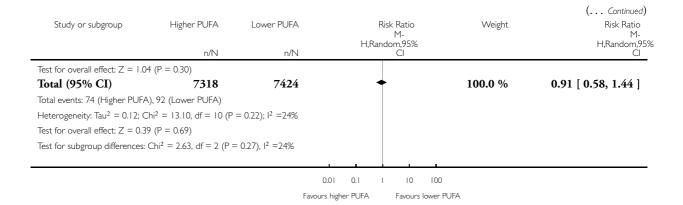


Analysis 1.33. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 33 Stroke - subgroup by sex.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 33 Stroke - subgroup by sex



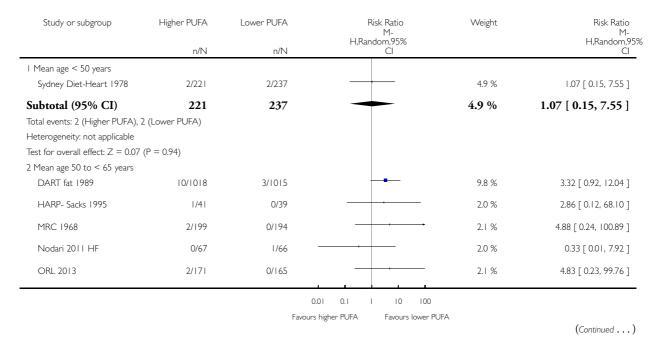


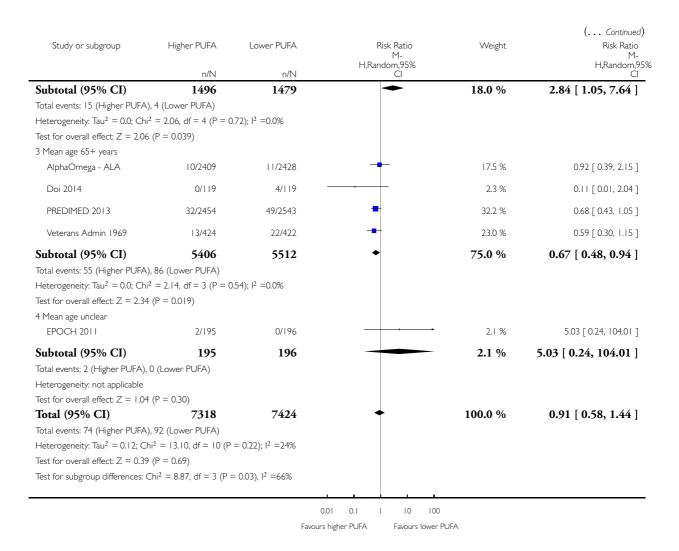
Analysis 1.34. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 34 Stroke - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 34 Stroke - subgroup by age



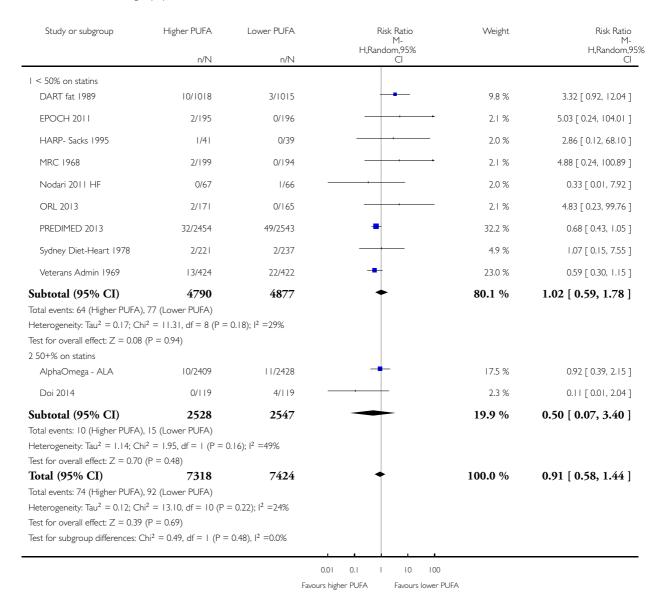


Analysis 1.35. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 35 Stroke - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

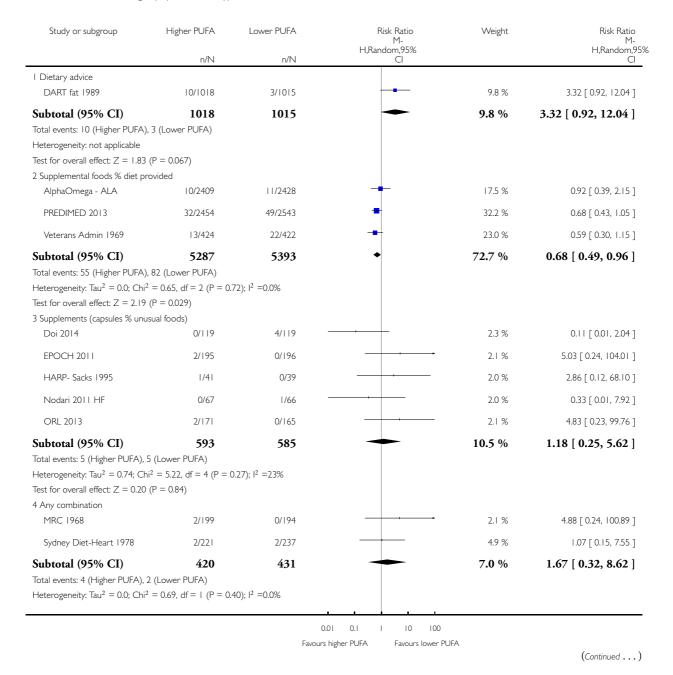
Outcome: 35 Stroke - subgroup by statin use



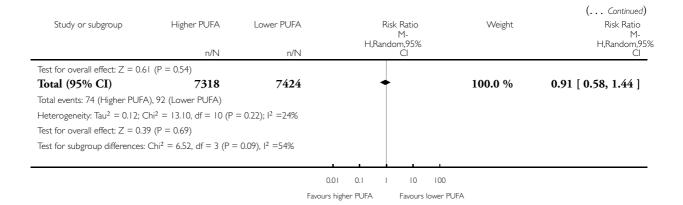
Analysis 1.36. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 36 Stroke - subgroup by intervention type.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 36 Stroke - subgroup by intervention type



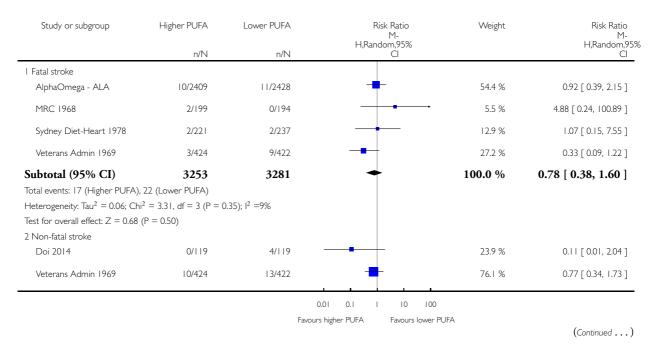
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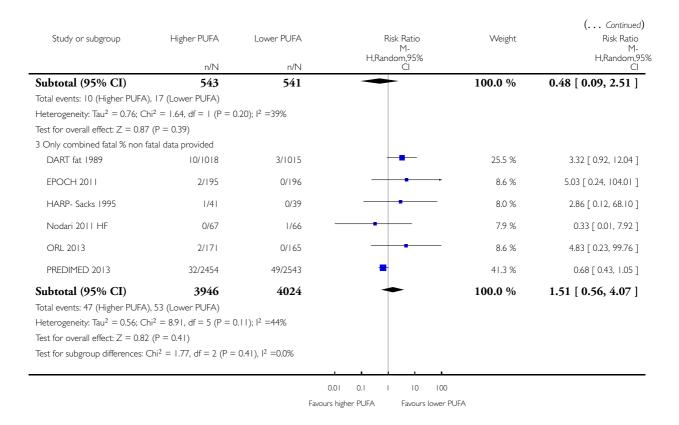


Analysis 1.37. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 37 Stroke - subgroup by fatal & non fatal.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 37 Stroke - subgroup by fatal % non fatal

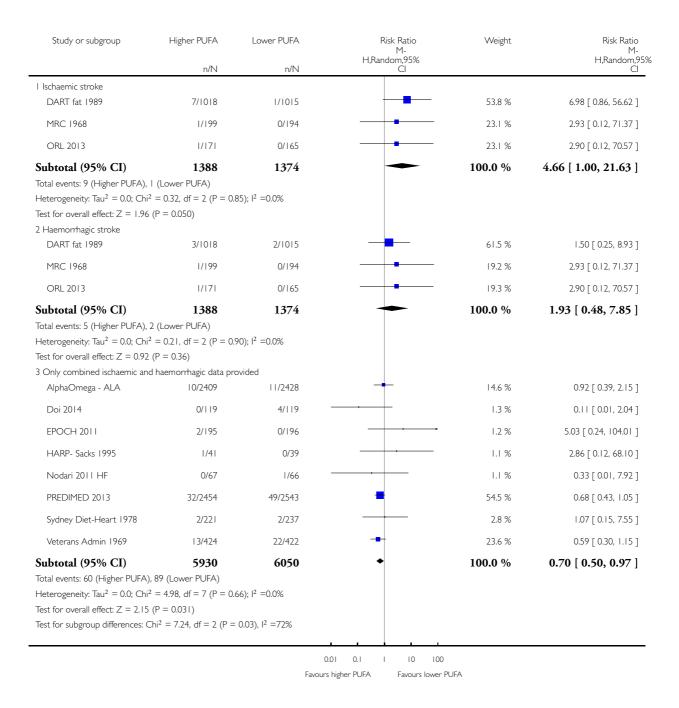




Analysis 1.38. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 38 Stroke - subgroup by ischaemic & haemorrhagic.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 38 Stroke - subgroup by ischaemic % haemorrhagic

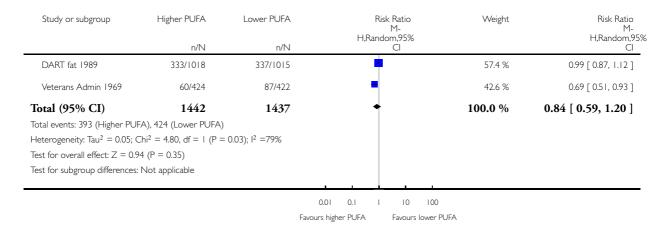


Analysis 1.39. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 39 MAJOR ADVERSE CARDIAC & CEREBROVASCULAR EVENTS (MACCEs).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

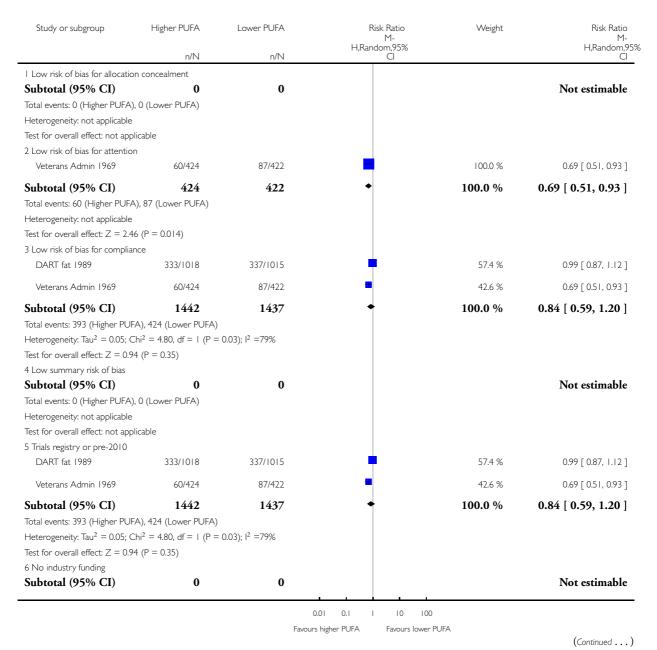
Outcome: 39 MAJOR ADVERSE CARDIAC % CEREBROVASCULAR EVENTS (MACCEs)

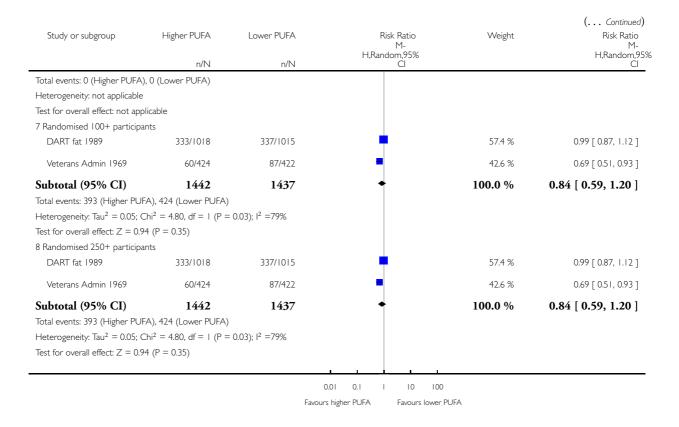


Analysis 1.40. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 40 MACCEs - SA.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 40 MACCEs - SA



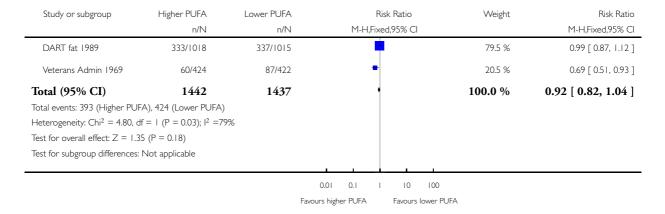


Analysis 1.41. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 41 MACCEs - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

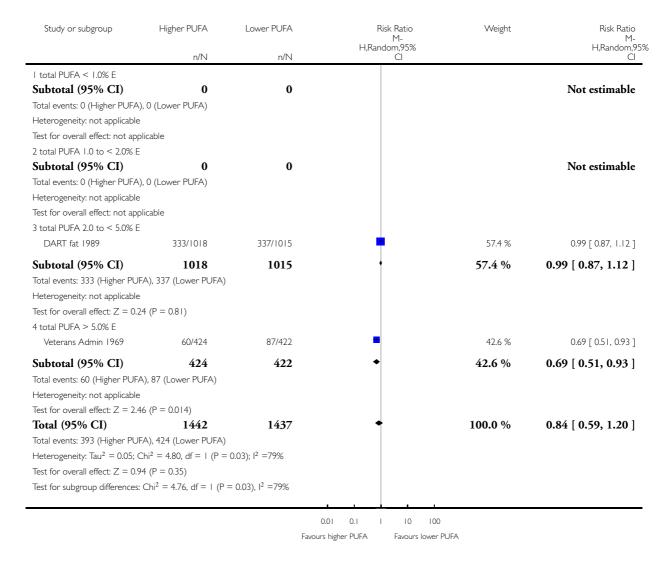
Outcome: 41 MACCEs - SA fixed-effect



Analysis 1.42. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 42 MACCEs - subgroup by PUFA dose.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

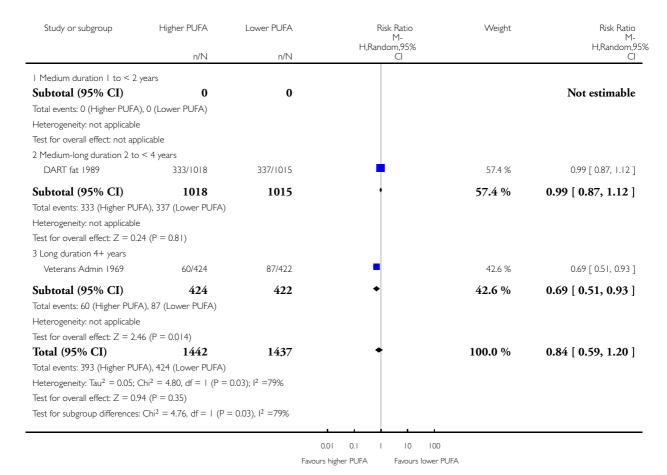
Outcome: 42 MACCEs - subgroup by PUFA dose



Analysis 1.43. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 43 MACCEs - subgroup by duration.

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 43 MACCEs - subgroup by duration

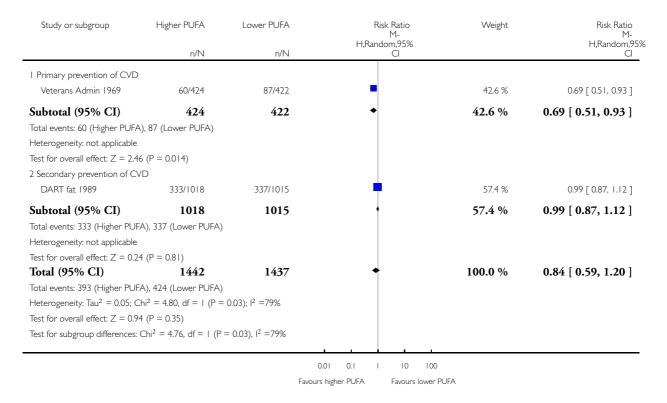


Analysis 1.44. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 44 MACCEs - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 44 MACCEs - subgroup by primary or secondary prevention

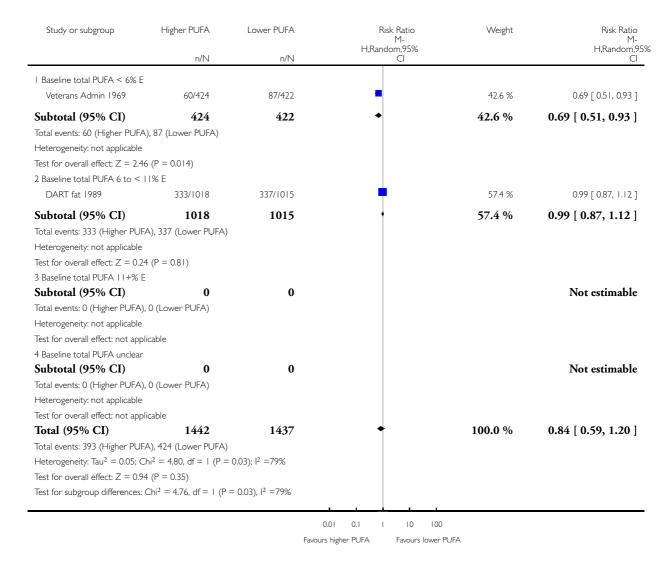


Analysis 1.45. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 45 MACCEs - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 45 MACCEs - subgroup by baseline PUFA dose

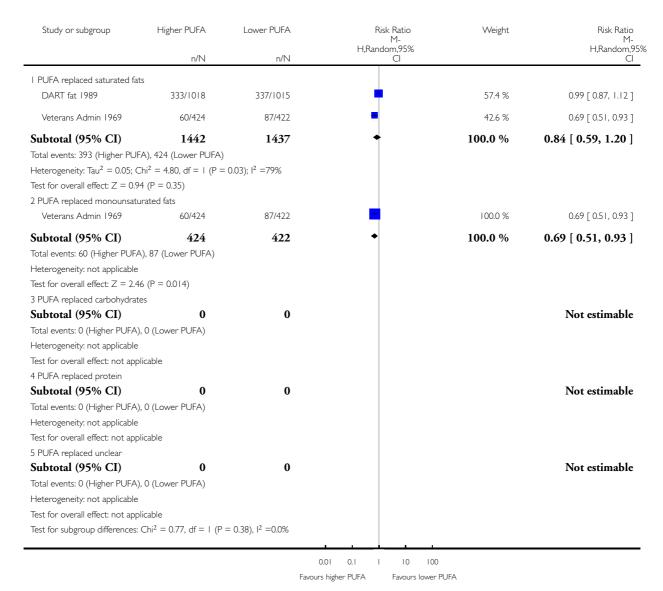


Analysis 1.46. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 46 MACCEs - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 46 MACCEs - subgroup by replacement



Analysis 1.47. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 47 MACCEs - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 47 MACCEs - subgroup by sex

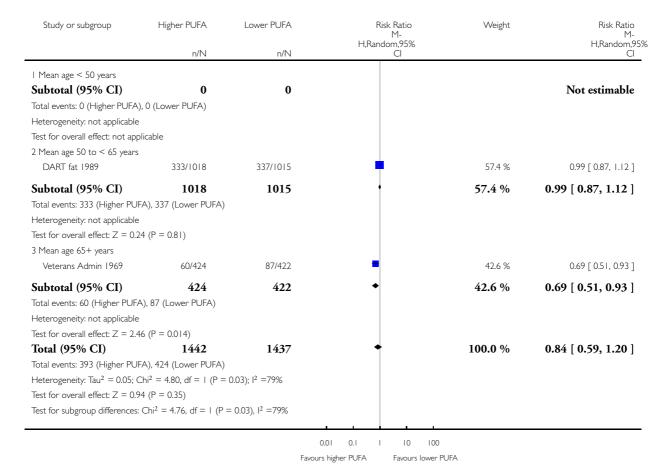


Analysis 1.48. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 48 MACCEs - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 48 MACCEs - subgroup by age

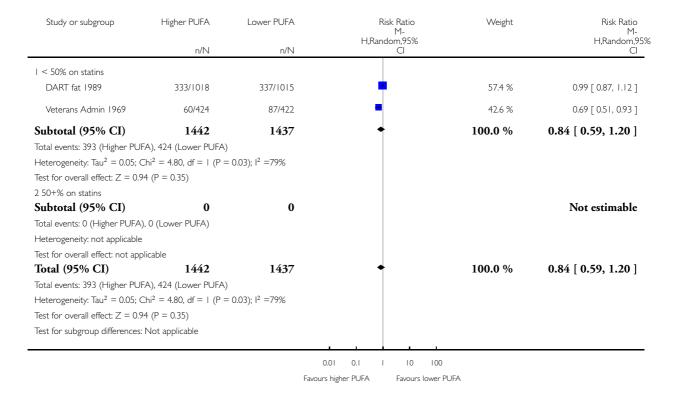


Analysis 1.49. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 49 MACCEs - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 49 MACCEs - subgroup by statin use

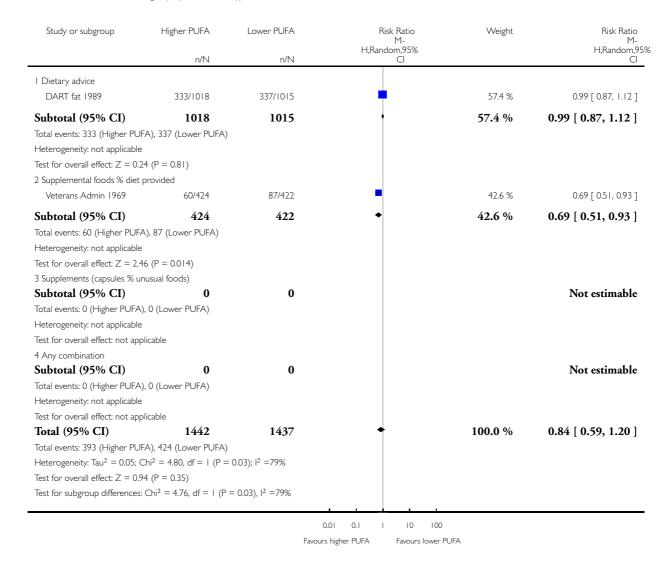


Analysis 1.50. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 50 MACCEs - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 50 MACCEs - subgroup by intervention type

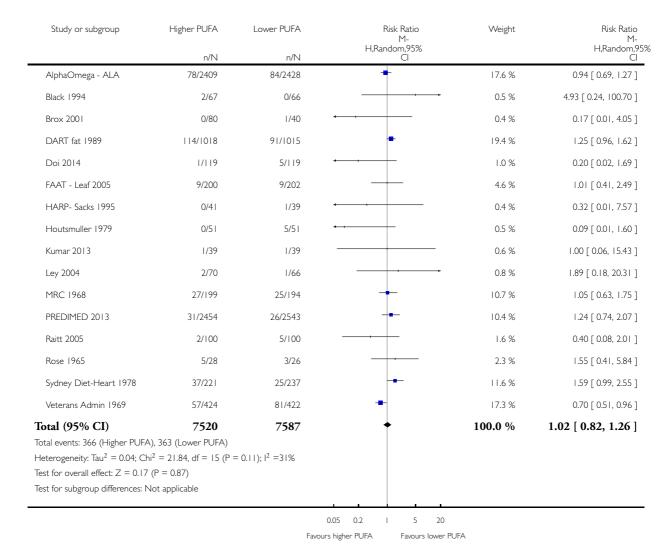


Analysis 2.1. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome I CARDIOVASCULAR MORTALITY.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: I CARDIOVASCULAR MORTALITY

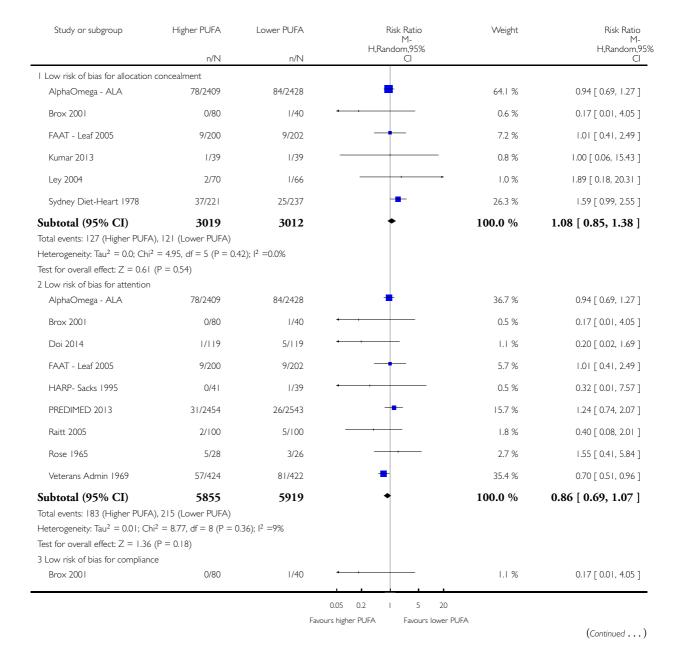


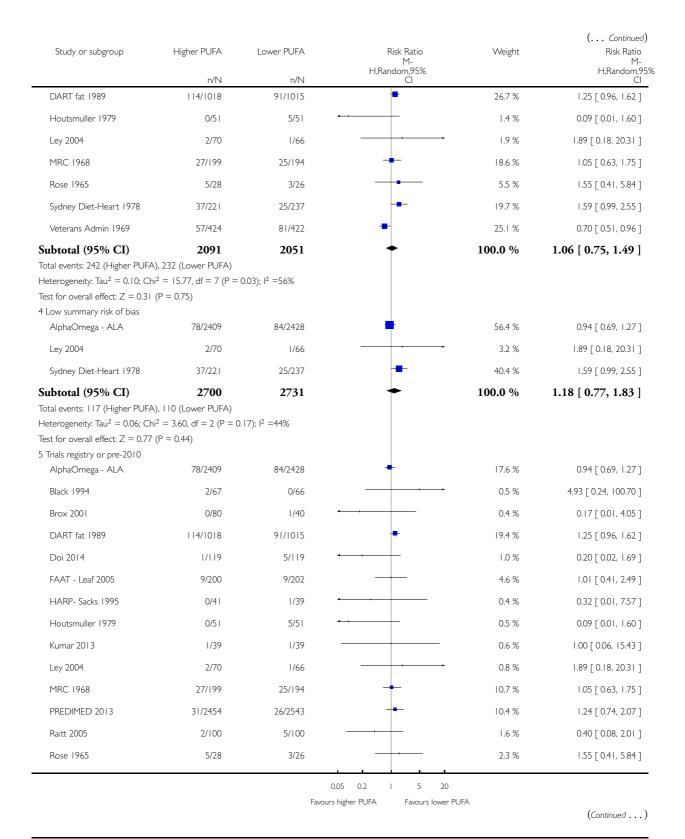
Analysis 2.2. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 2 Cardiovascular mortality - SA.

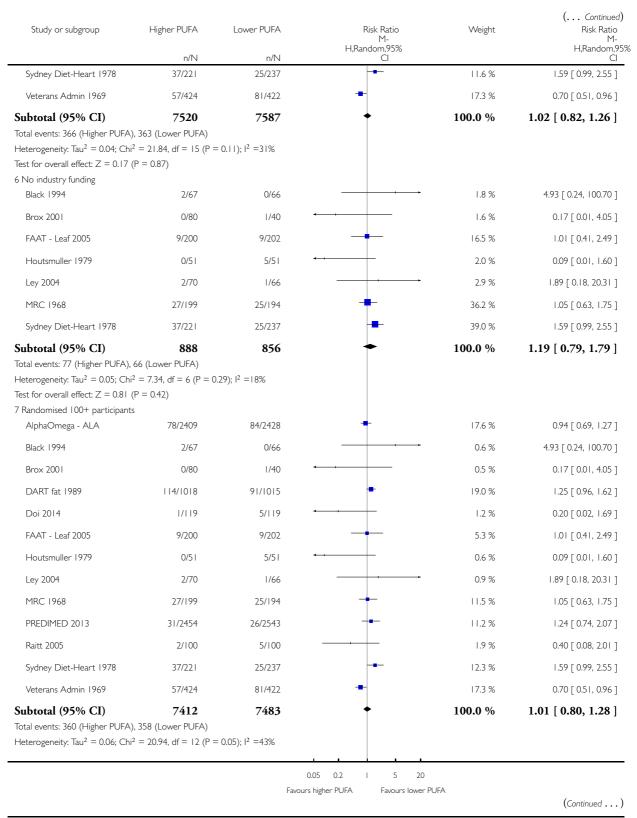
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

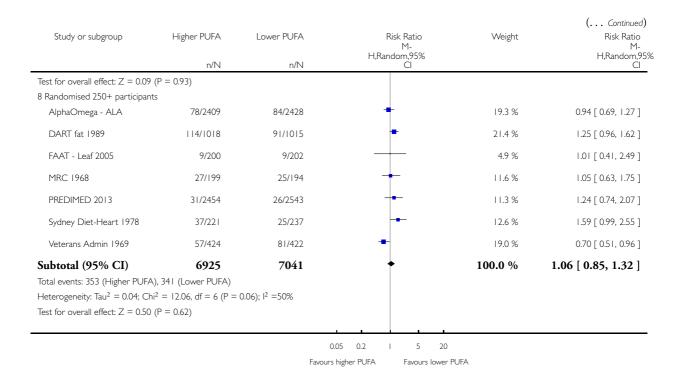
Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 2 Cardiovascular mortality - SA







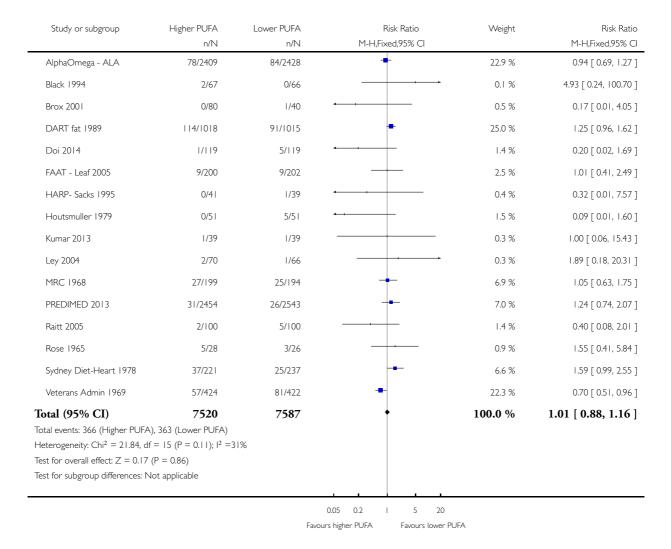


Analysis 2.3. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 3 Cardiovascular mortality - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 3 Cardiovascular mortality - SA fixed-effect

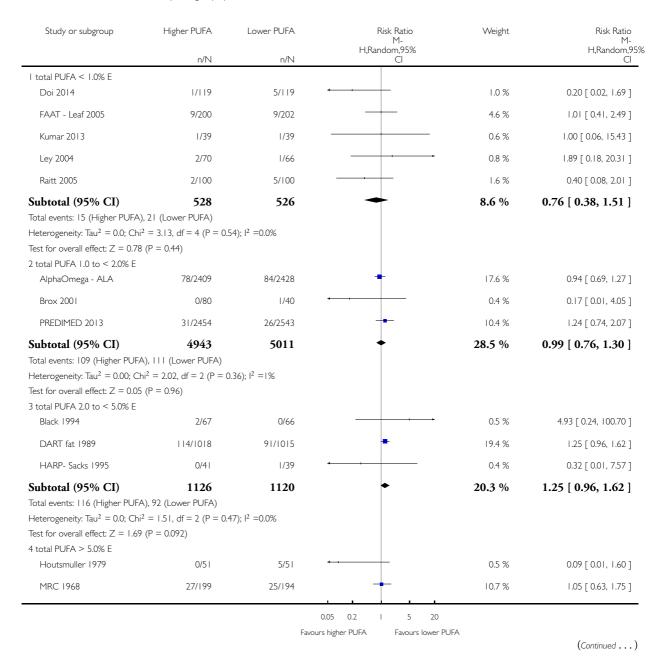


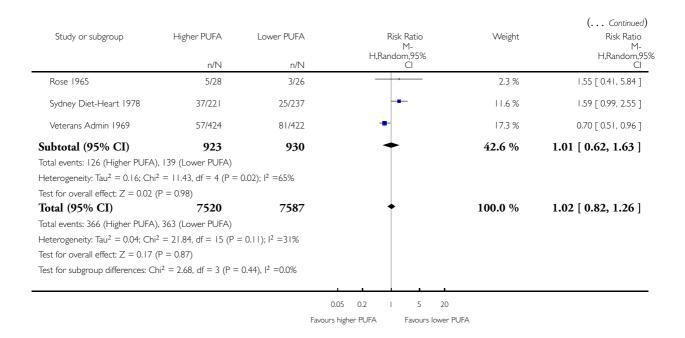
Analysis 2.4. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 4 Cardiovascular mortality - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 4 Cardiovascular mortality - subgroup by PUFA dose



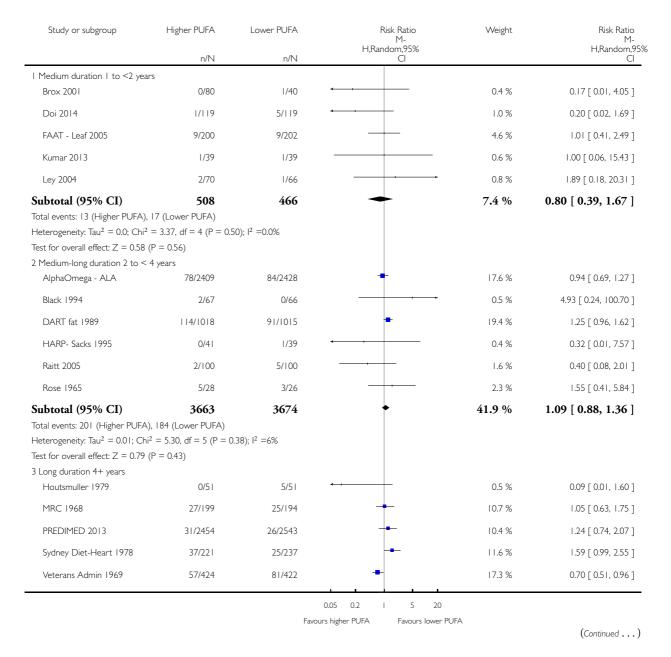


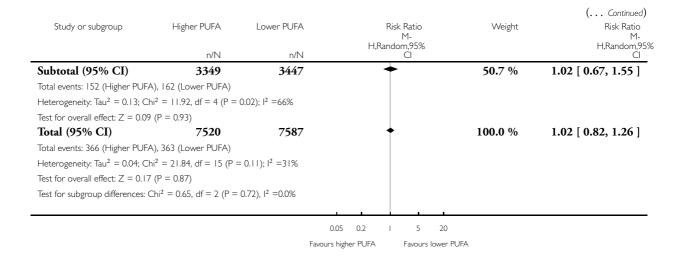
Analysis 2.5. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 5

Cardiovascular mortality - subgroup by duration.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 5 Cardiovascular mortality - subgroup by duration



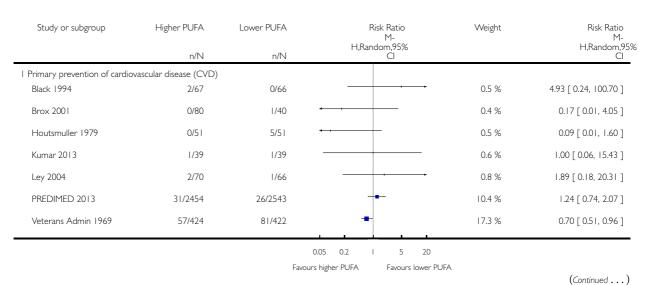


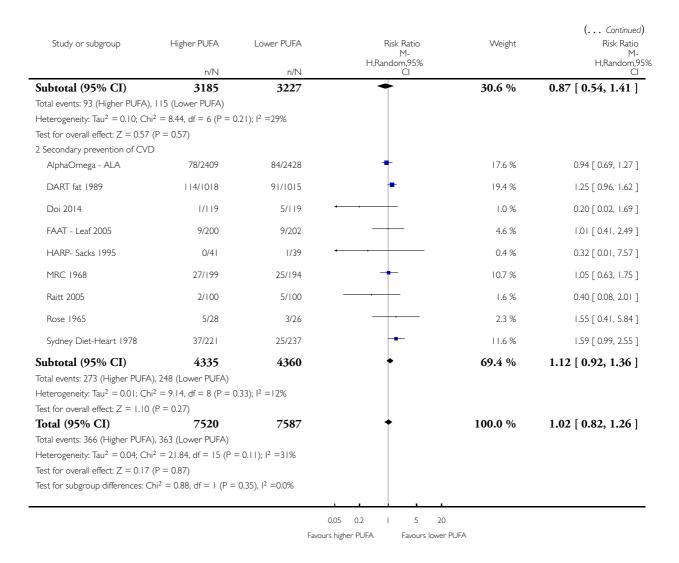
Analysis 2.6. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 6 Cardiovascular mortality - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 6 Cardiovascular mortality - subgroup by primary or secondary prevention



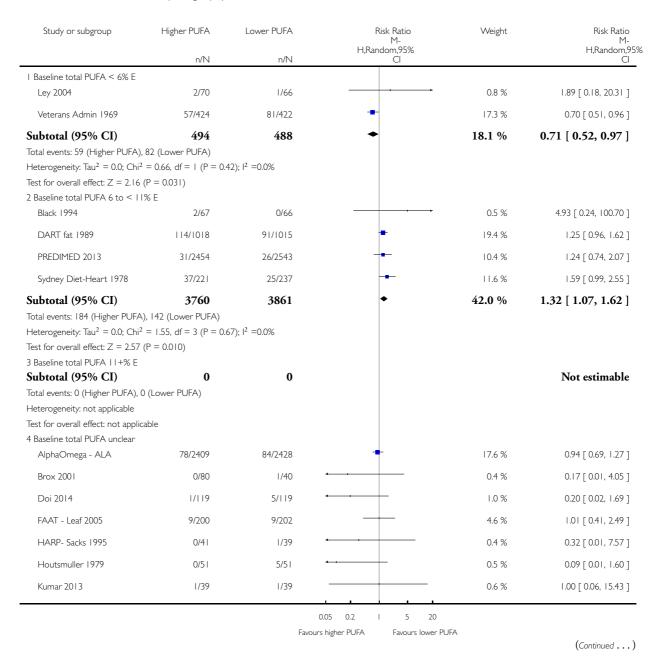


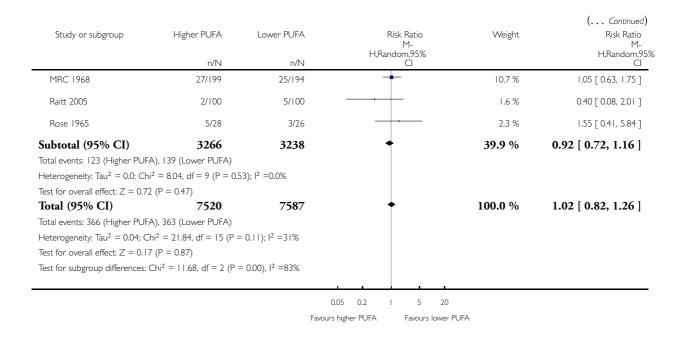
Analysis 2.7. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 7

Cardiovascular mortality - subgroup by baseline PUFA dose.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 7 Cardiovascular mortality - subgroup by baseline PUFA dose



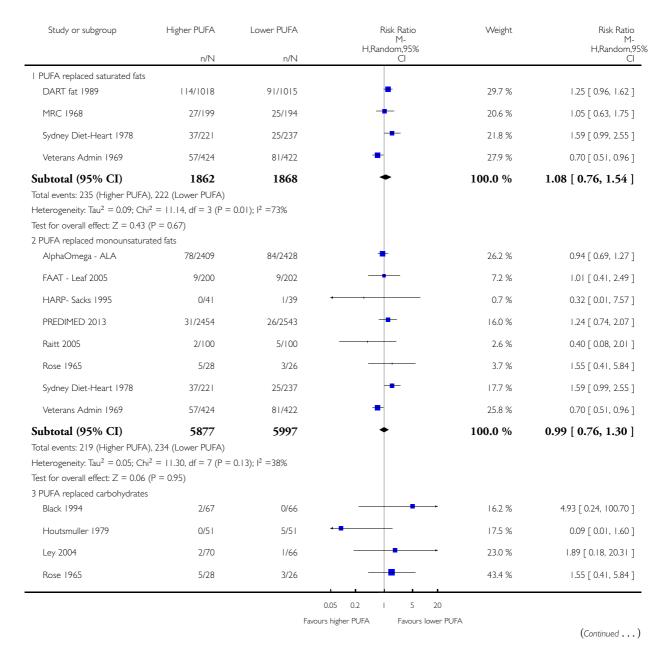


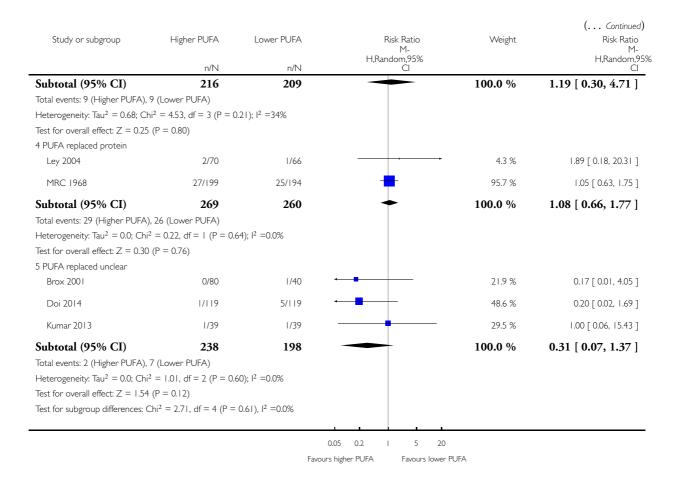
Analysis 2.8. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 8

Cardiovascular mortality - subgroup by replacement.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 8 Cardiovascular mortality - subgroup by replacement



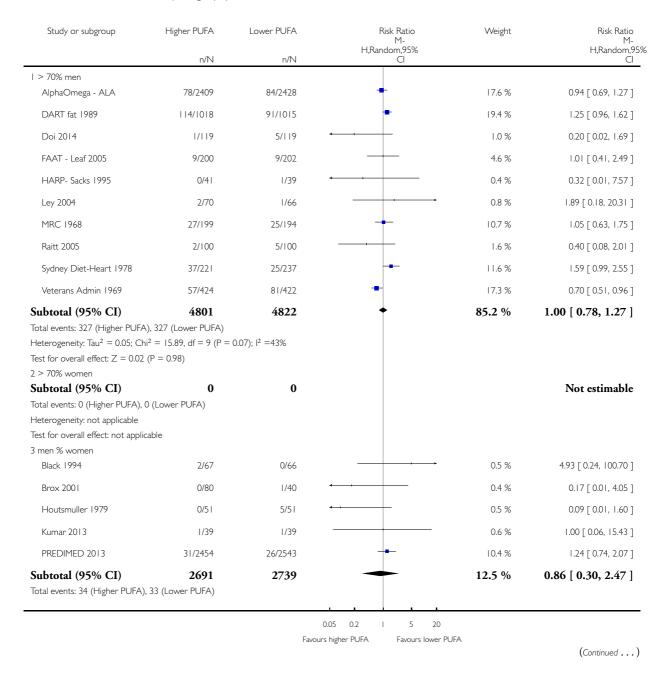


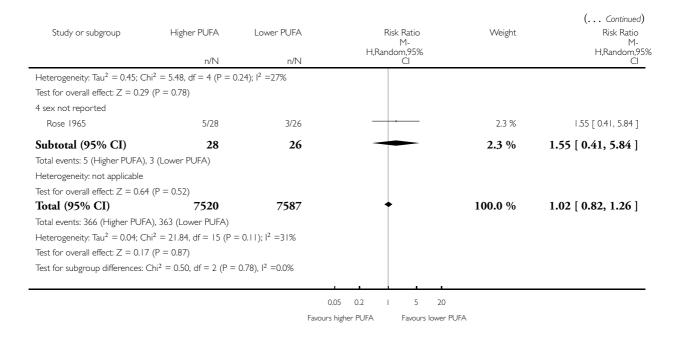
Analysis 2.9. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 9

Cardiovascular mortality - subgroup by sex.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 9 Cardiovascular mortality - subgroup by sex

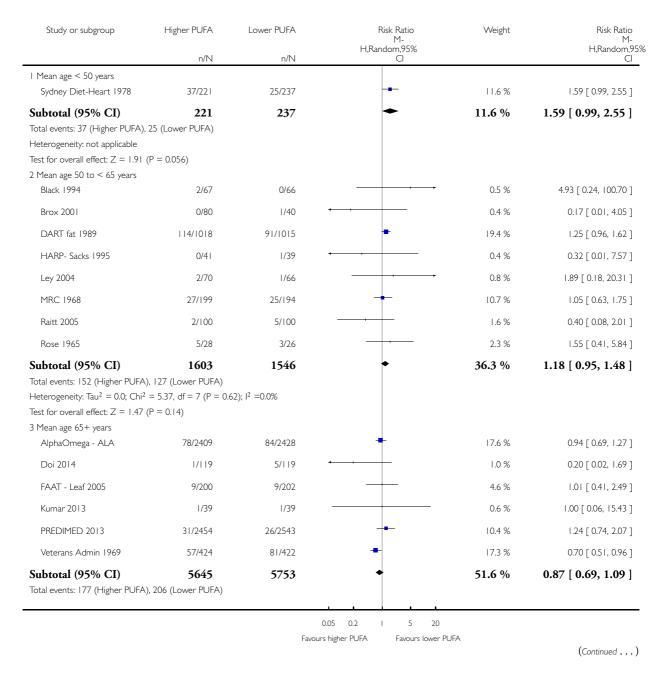


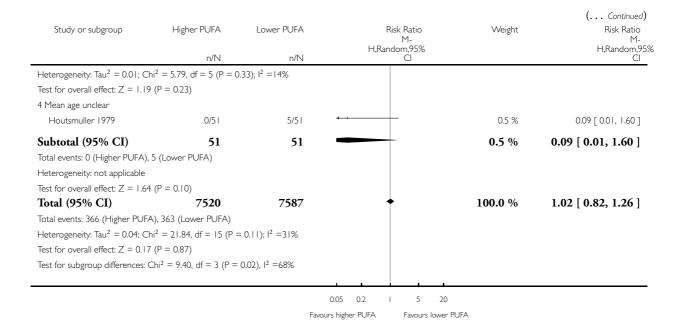


Analysis 2.10. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 10 Cardiovascular mortality - subgroup by age.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 10 Cardiovascular mortality - subgroup by age

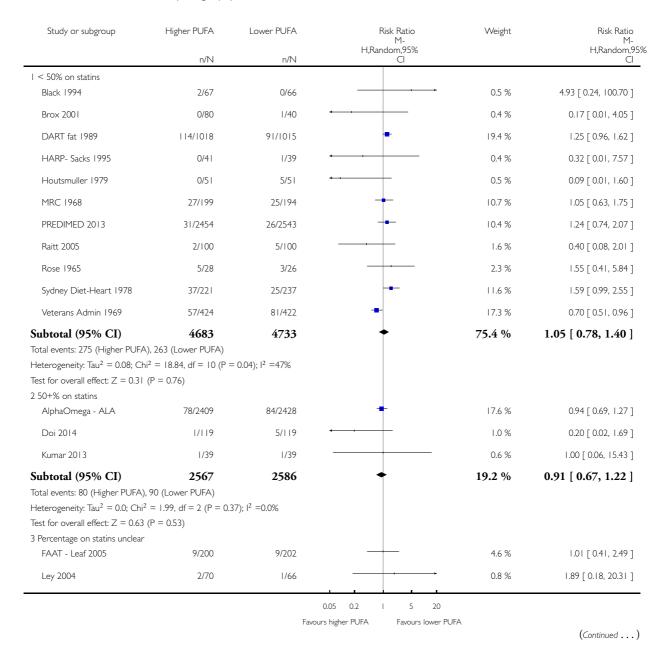


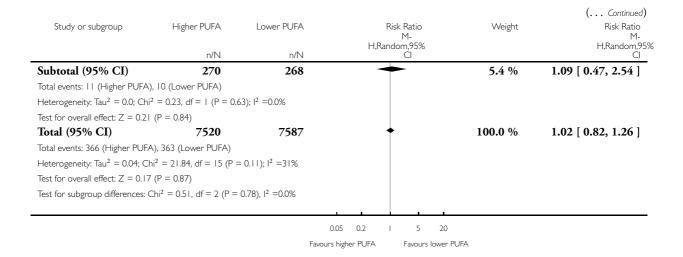


Analysis 2.11. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 11 Cardiovascular mortality - subgroup by statin use.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: II Cardiovascular mortality - subgroup by statin use



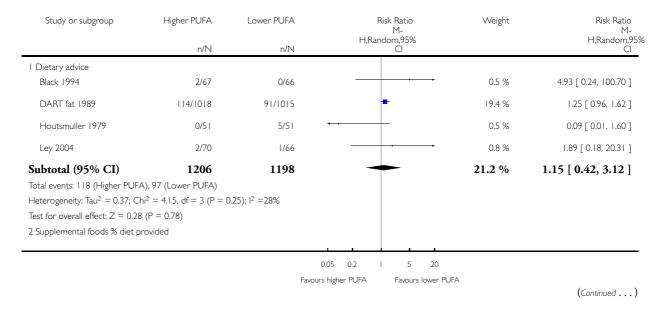


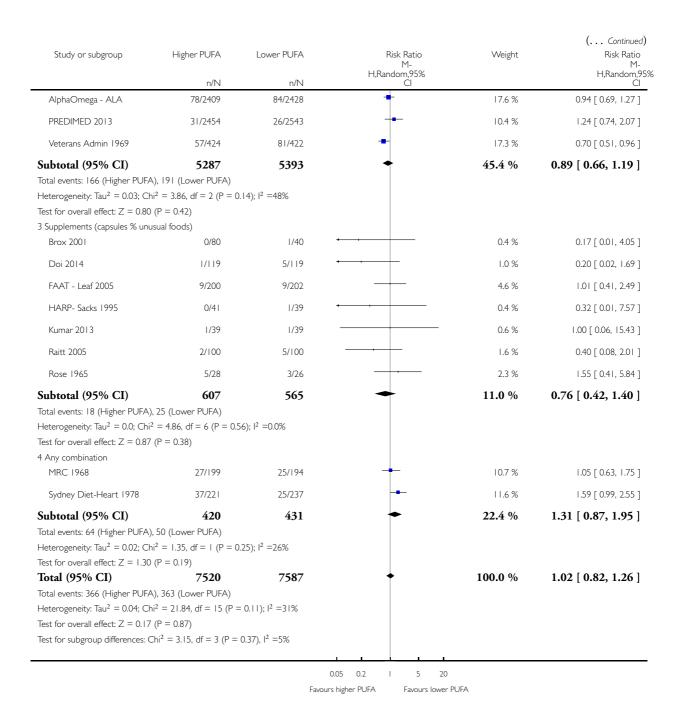
Analysis 2.12. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 12 Cardiovascular mortality - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 12 Cardiovascular mortality - subgroup by intervention type



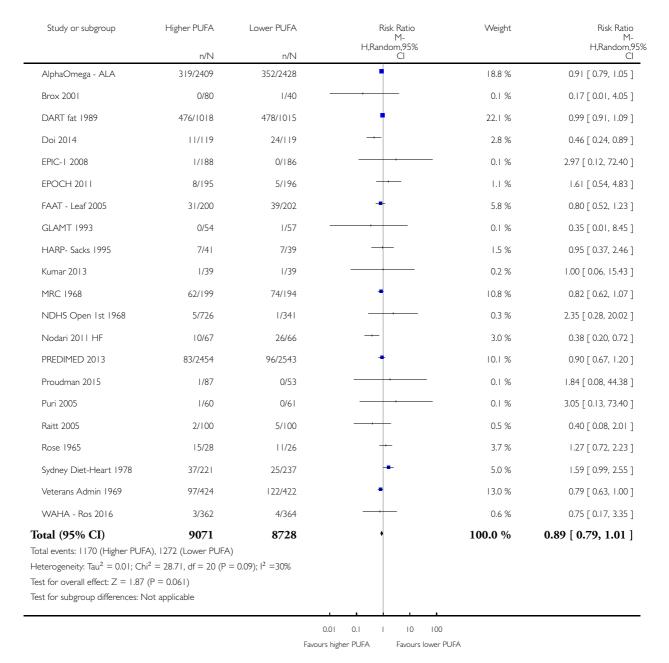


Analysis 2.13. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 13 CARDIOVASCULAR EVENTS.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

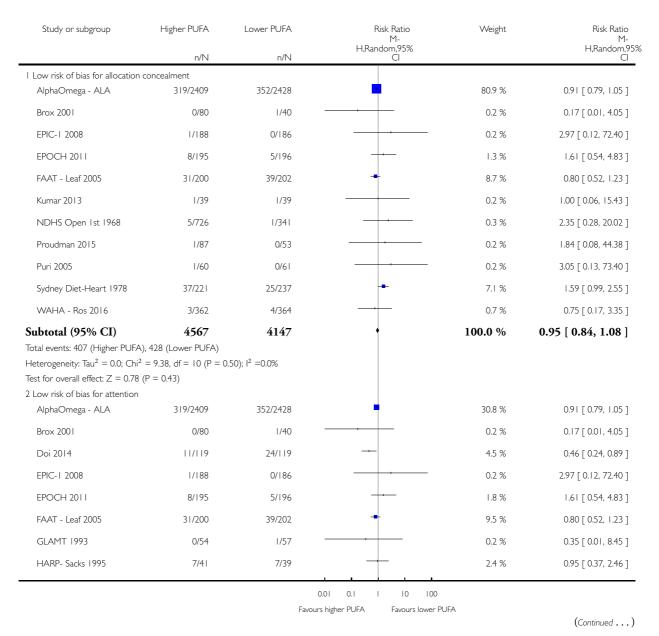
Outcome: 13 CARDIOVASCULAR EVENTS

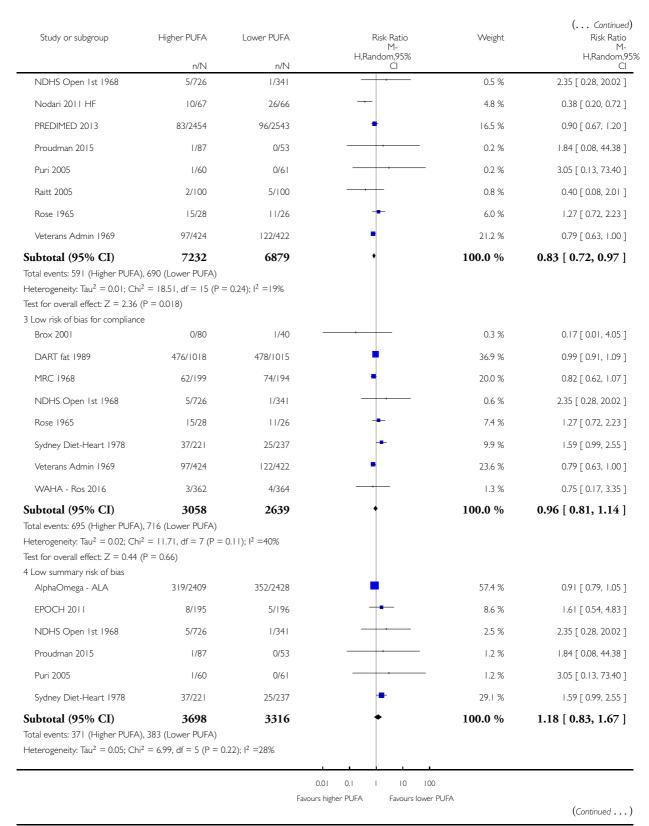


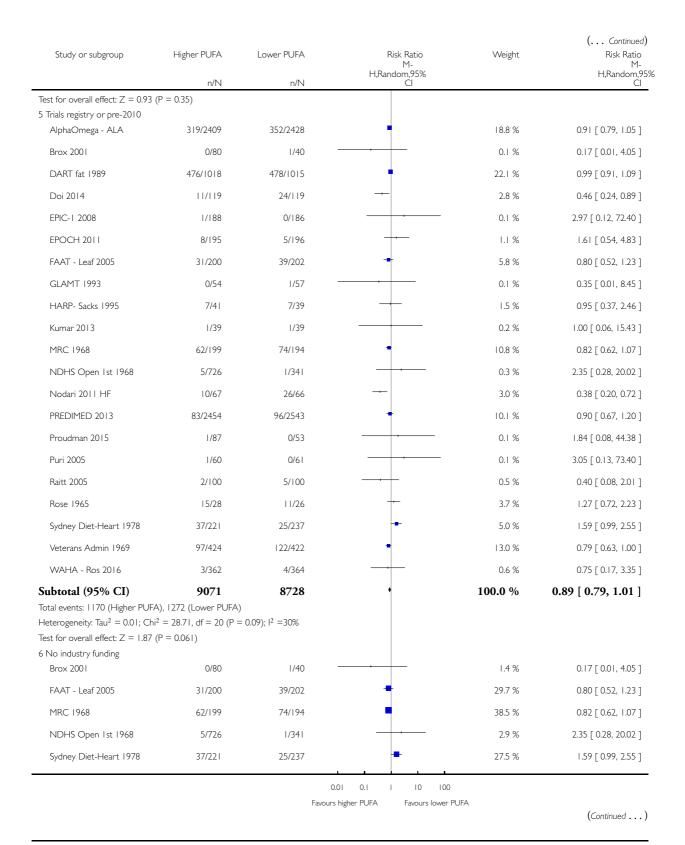
Analysis 2.14. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 14 CVD events - SA.

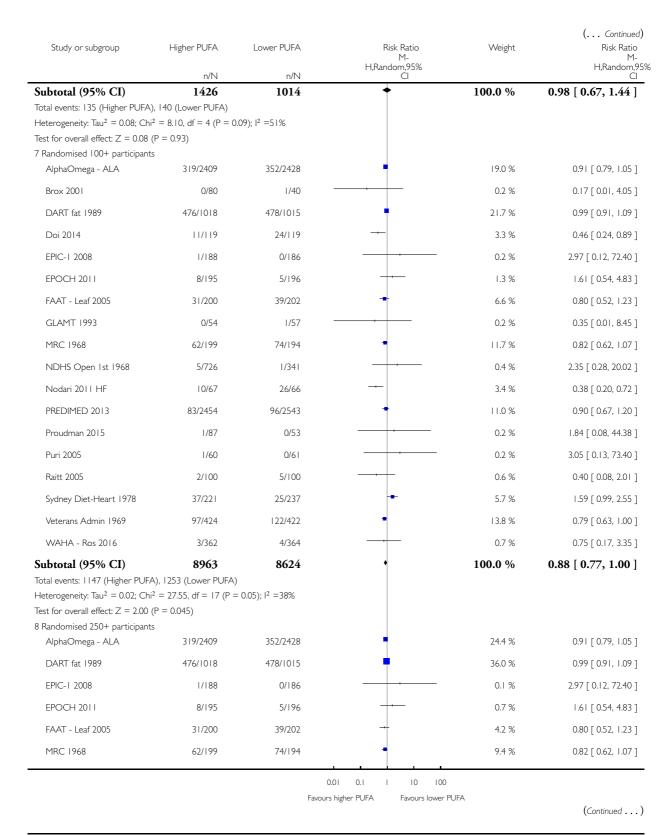
Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

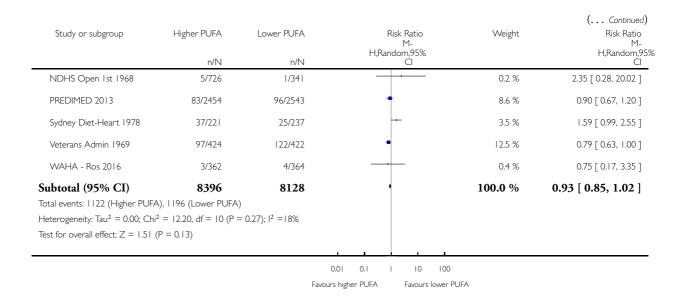
Outcome: 14 CVD events - SA









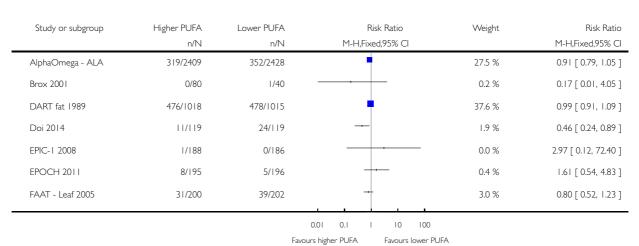


Analysis 2.15. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 15 CVD events - SA fixed-effect.

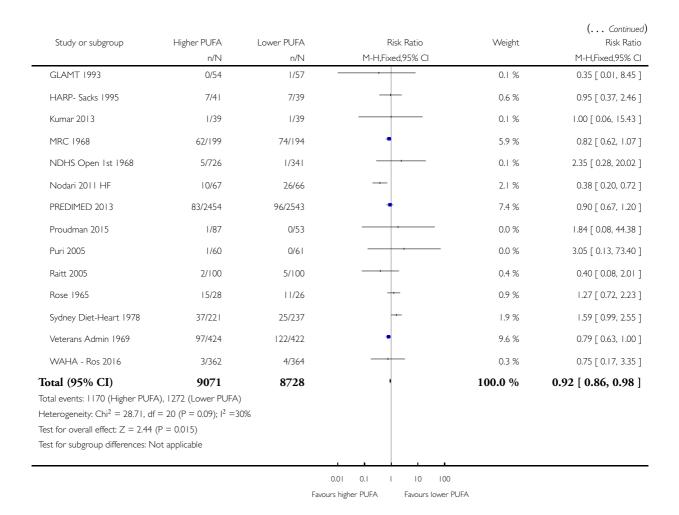
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 15 CVD events - SA fixed-effect



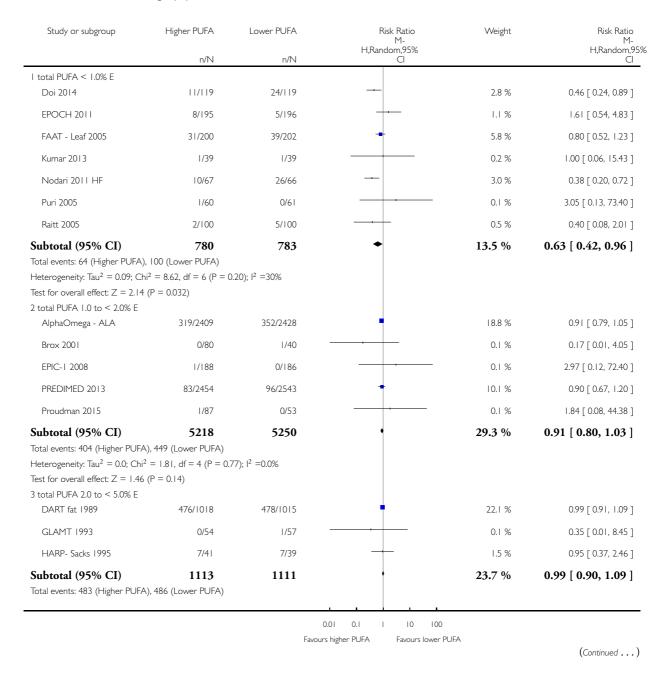
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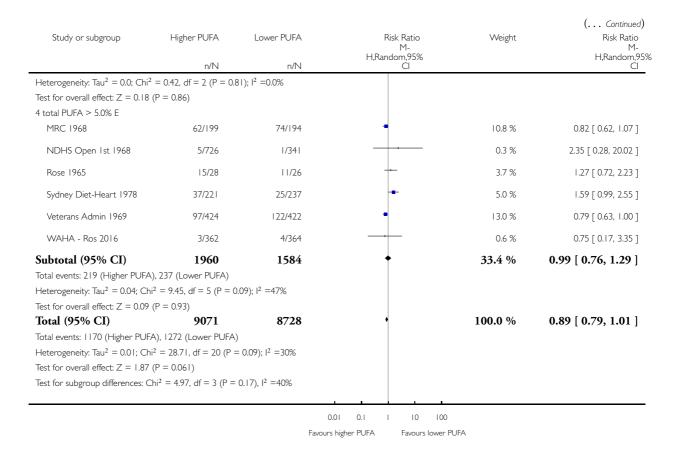


Analysis 2.16. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 16 CVD events - subgroup by PUFA dose.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 16 CVD events - subgroup by PUFA dose

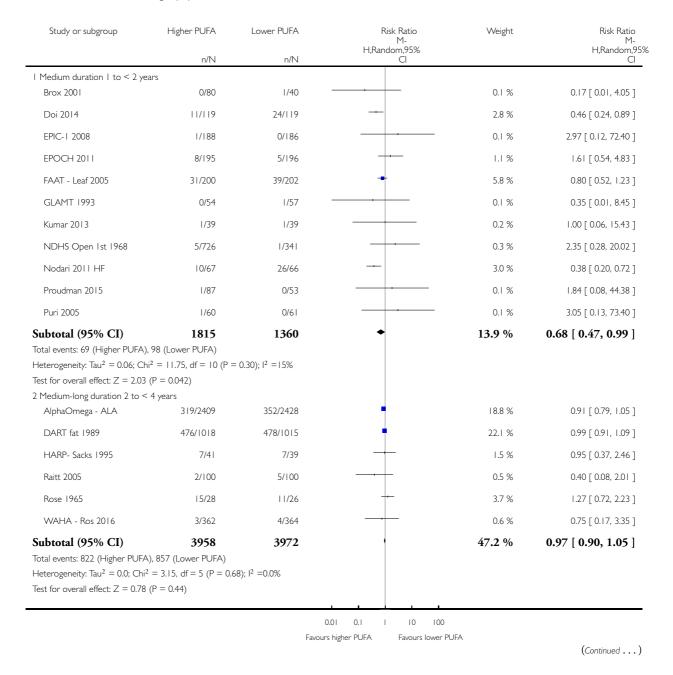




Analysis 2.17. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 17 CVD events - subgroup by duration.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 17 CVD events - subgroup by duration

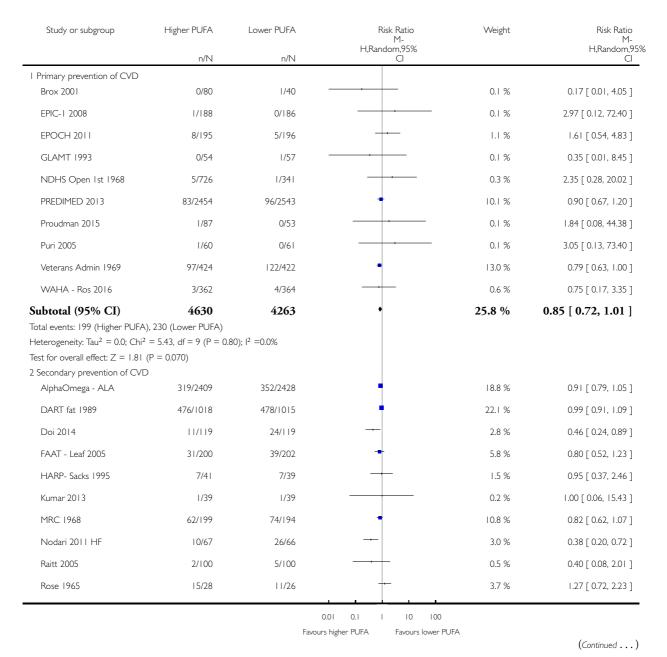


Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95% C1	Weight	(Continued) Risk Ratio M- H,Random,95%
3 Long duration 4+ years	11/17	11/11	CI		<u> </u>
MRC 1968	62/199	74/194	-	10.8 %	0.82 [0.62, 1.07]
PREDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [0.67, 1.20]
Sydney Diet-Heart 1978	37/221	25/237	-	5.0 %	1.59 [0.99, 2.55]
Veterans Admin 1969	97/424	122/422	-	13.0 %	0.79 [0.63, 1.00]
Subtotal (95% CI)	3298	3396	•	38.9 %	0.92 [0.73, 1.16]
Total events: 279 (Higher PUFA	.), 317 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.03$; Ch	$i^2 = 7.12$, df = 3 (P = 0).07); I ² =58%			
Test for overall effect: $Z = 0.72$	(P = 0.47)				
Total (95% CI)	9071	8728	•	100.0 %	0.89 [0.79, 1.01]
Total events: 1170 (Higher PUF.	A), 1272 (Lower PUFA)			
Heterogeneity: Tau ² = 0.01; Ch	$i^2 = 28.7 I$, $df = 20 (P = 20) I$	= 0.09); I ² =30%			
Test for overall effect: $Z = 1.87$	(P = 0.061)				
Test for subgroup differences: C	$2 \text{hi}^2 = 3.48, \text{ df} = 2 \text{ (P} = 2)$	0.18), 12 =43%			
			0.01 0.1 1 10 100		
			Favours higher PUFA Favours lower F	UFA	

Analysis 2.18. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 18 CVD events - subgroup by primary or secondary prevention.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 18 CVD events - subgroup by primary or secondary prevention



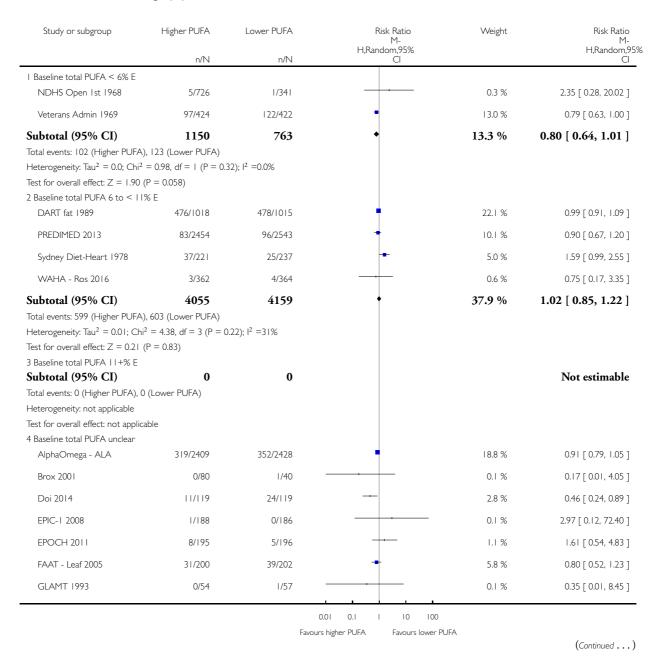
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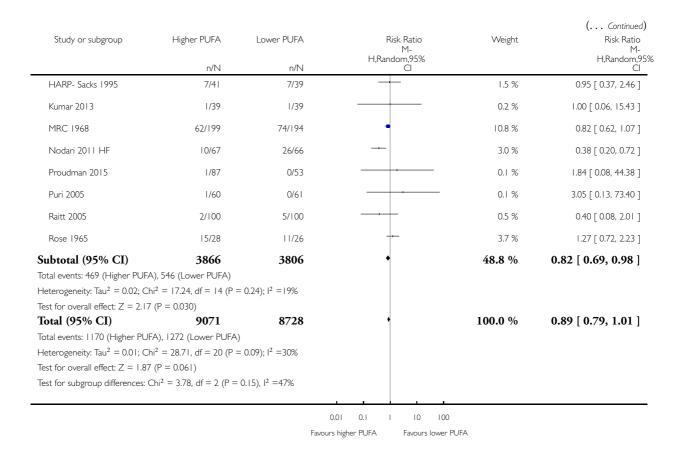
						(Continued)
Study or subgroup	Higher PUFA	Lower PUFA	Ri	sk Ratio	Weight	Risk Ratio
			H Rano	M- dom,95%		M- H,Random,95%
	n/N	n/N	i i,i vario	Cl		Cl
Sydney Diet-Heart 1978	37/221	25/237		-	5.0 %	1.59 [0.99, 2.55]
Subtotal (95% CI)	4441	4465	•		74.2 %	0.89 [0.75, 1.05]
Total events: 971 (Higher PUFA),	1042 (Lower PUFA)					
Heterogeneity: Tau ² = 0.03; Chi ²	= 22.10, df = 10 (P =	= 0.01); I ² =55%				
Test for overall effect: $Z = 1.43$ (F	P = 0.15)					
Total (95% CI)	9071	8728	•		100.0 %	0.89 [0.79, 1.01]
Total events: 1170 (Higher PUFA)	ı, 1272 (Lower PUFA)				
Heterogeneity: Tau ² = 0.01; Chi ²	= 28.71, df = 20 (P	= 0.09); I ² =30%				
Test for overall effect: $Z = 1.87$ (F	9 = 0.061)					
Test for subgroup differences: Chi	2 = 0.11, df = 1 (P =	0.74), I ² =0.0%				
			0.01 0.1 1	10 100		
			Favours higher PUFA	Favours lower P	UFA	

Analysis 2.19. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 19 CVD events - subgroup by baseline PUFA dose.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 19 CVD events - subgroup by baseline PUFA dose

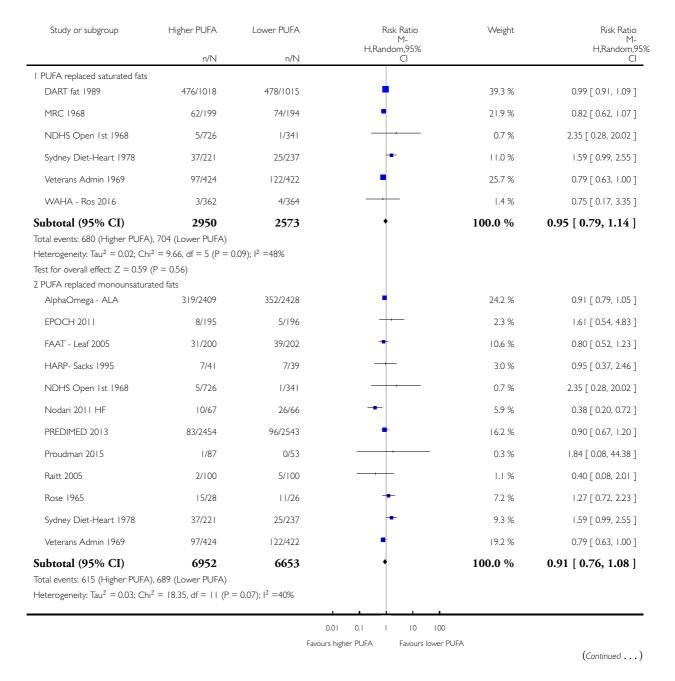


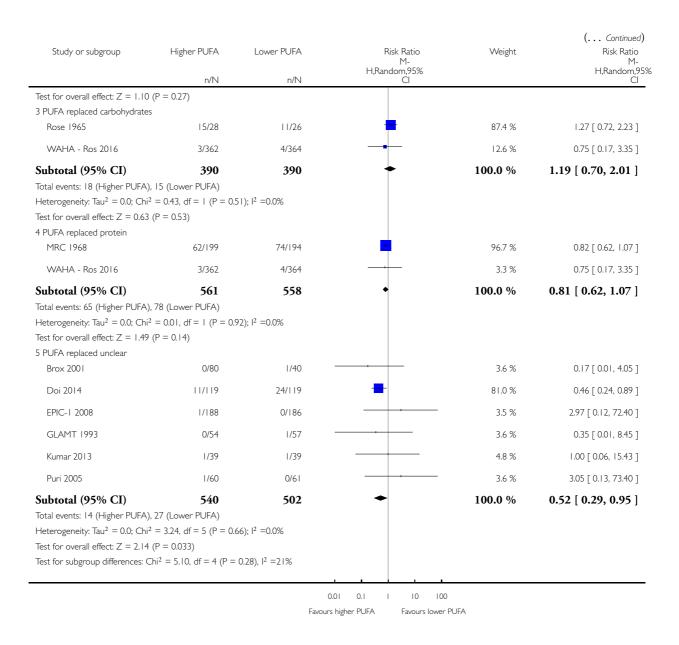


Analysis 2.20. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 20 CVD events - subgroup by replacement.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 20 CVD events - subgroup by replacement

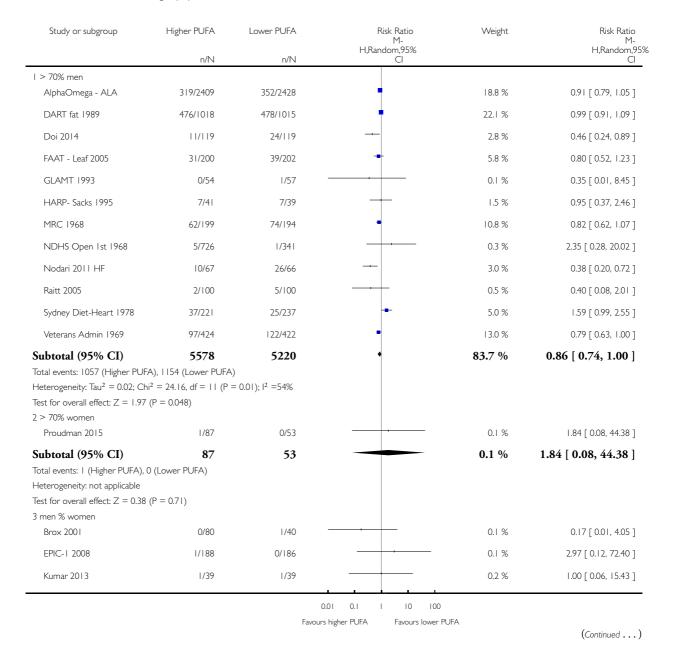


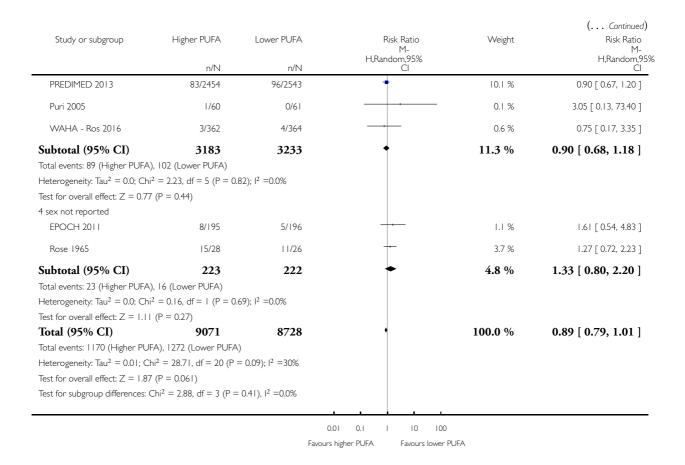


Analysis 2.21. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 21 CVD events - subgroup by sex.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 21 CVD events - subgroup by sex

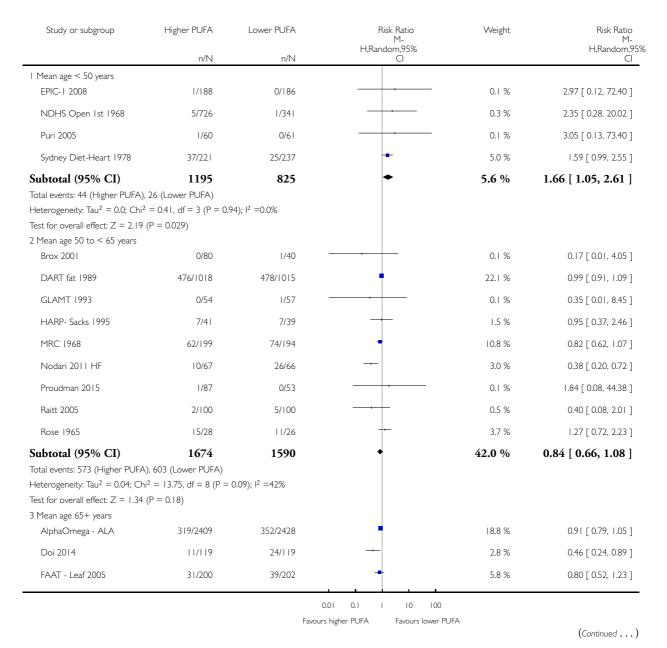


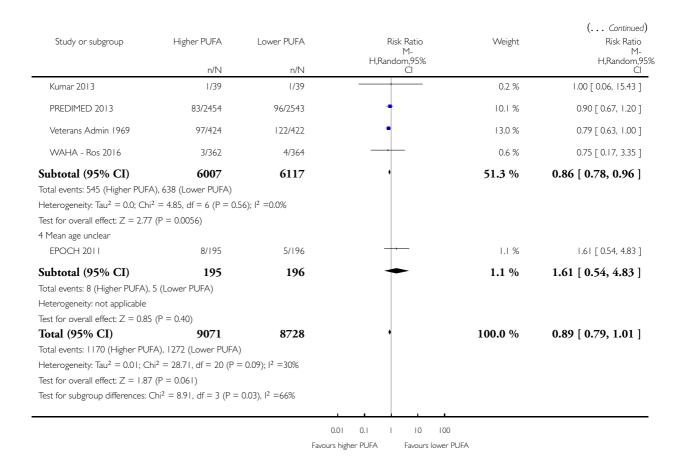


Analysis 2.22. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 22 CVD events - subgroup by age.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 22 CVD events - subgroup by age

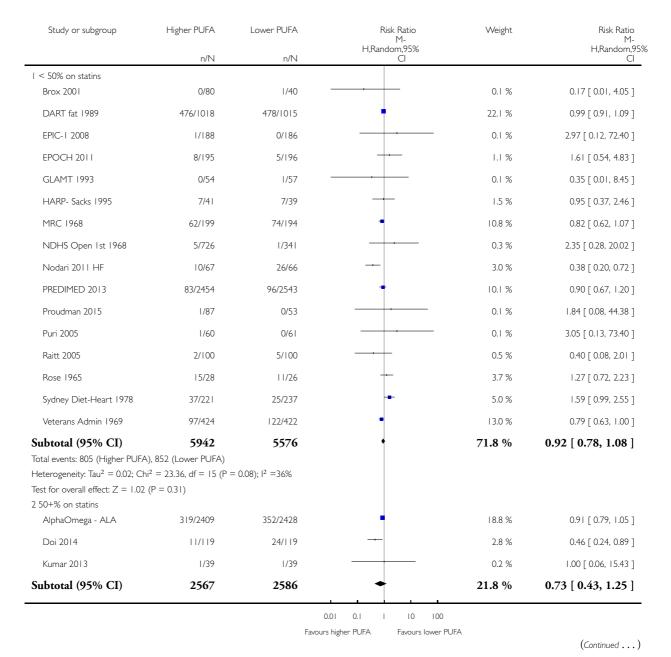




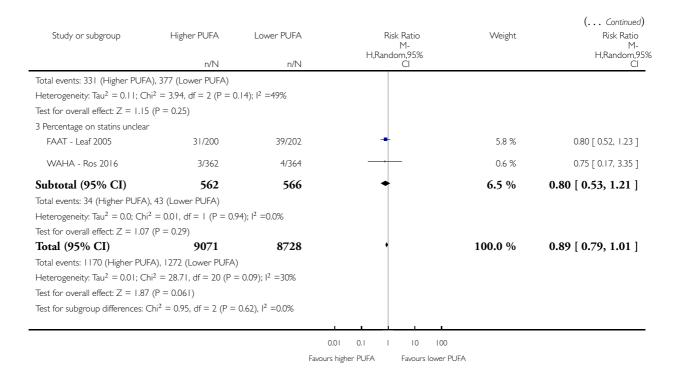
Analysis 2.23. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 23 CVD events - subgroup by statin use.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 23 CVD events - subgroup by statin use



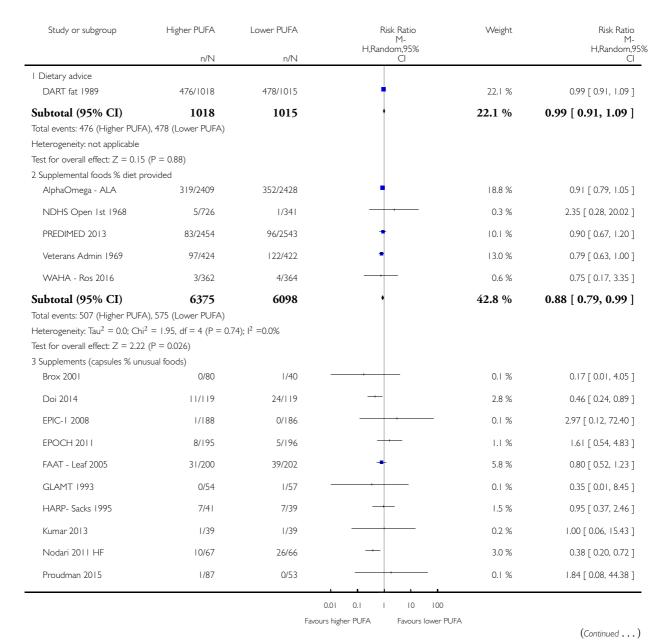
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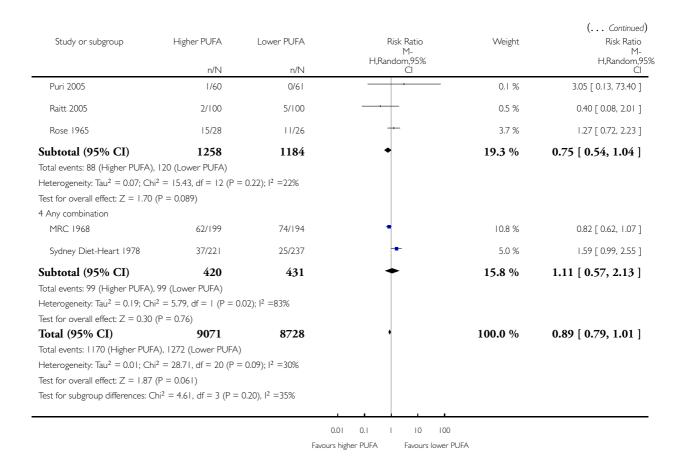
Analysis 2.24. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 24 CVD events - subgroup by intervention type.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 24 CVD events - subgroup by intervention type



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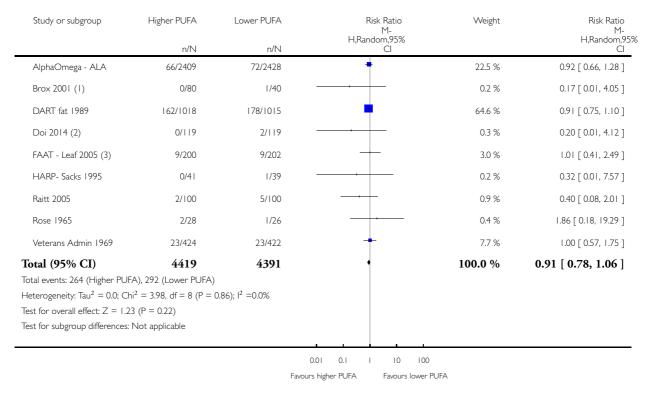


Analysis 2.25. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 25 CORONARY HEART DISEASE (CHD) MORTALITY.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 25 CORONARY HEART DISEASE (CHD) MORTALITY



⁽I) Fatal MI

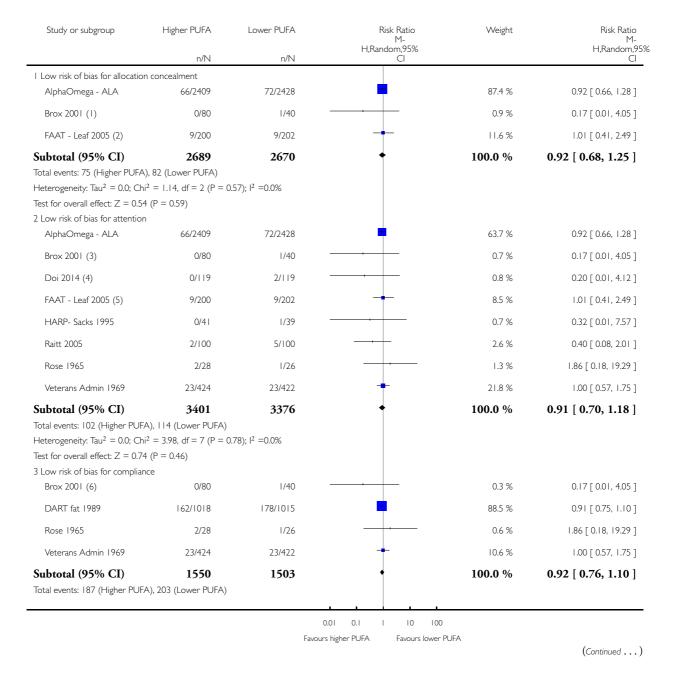
⁽²⁾ Fatal MI/ sudden death

⁽³⁾ Cardiac deaths

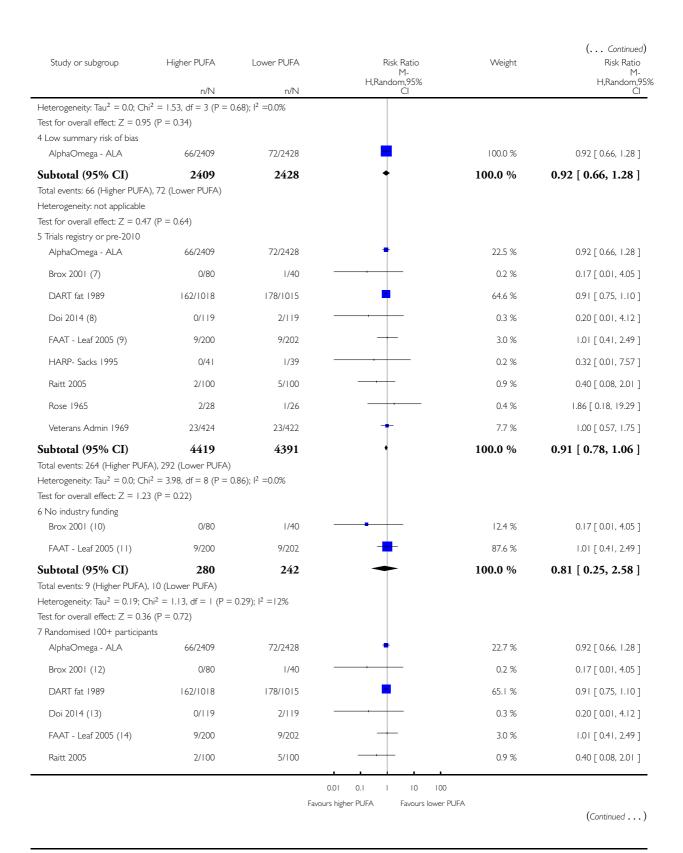
Analysis 2.26. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 26 CHD mortality - SA.

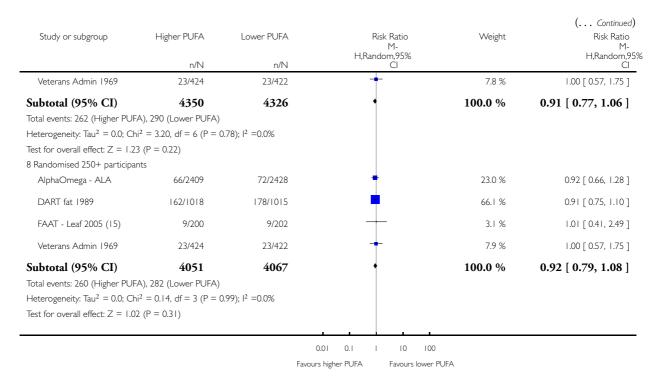
Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 26 CHD mortality - SA



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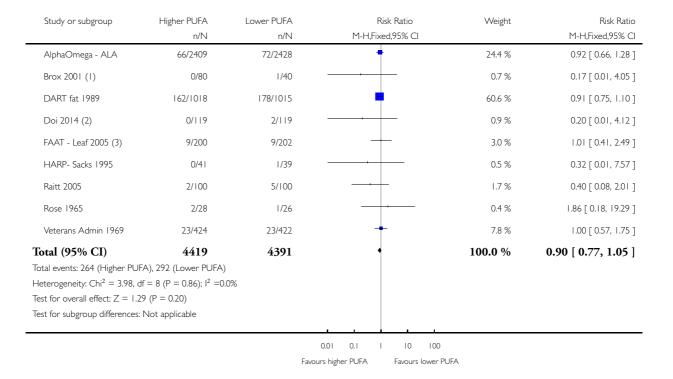
- (I) Fatal MI
- (2) Cardiac deaths
- (3) Fatal MI
- (4) Fatal MI/ sudden death
- (5) Cardiac deaths
- (6) Fatal MI
- (7) Fatal MI
- (8) Fatal MI/ sudden death
- (9) Cardiac deaths
- (10) Fatal MI
- (11) Cardiac deaths
- (12) Fatal MI
- (13) Fatal MI/ sudden death
- (14) Cardiac deaths
- (15) Cardiac deaths

Analysis 2.27. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 27 CHD mortality - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 27 CHD mortality - SA fixed-effect



⁽I) Fatal MI

⁽²⁾ Fatal MI/ sudden death

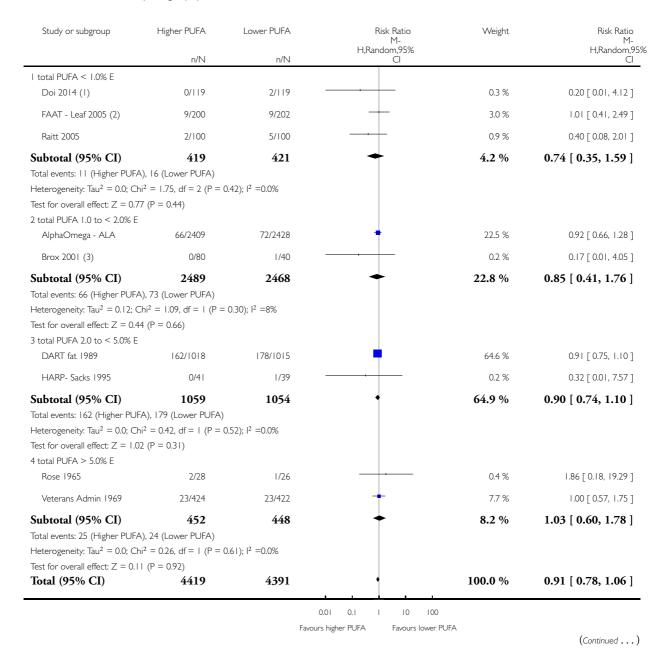
⁽³⁾ Cardiac deaths

Analysis 2.28. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 28 CHD mortality - subgroup by PUFA dose.

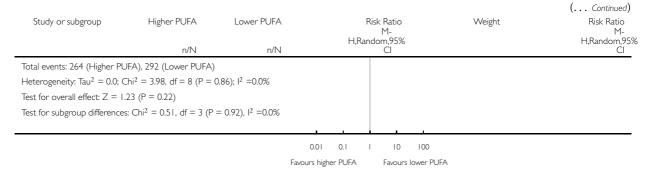
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 28 CHD mortality - subgroup by PUFA dose



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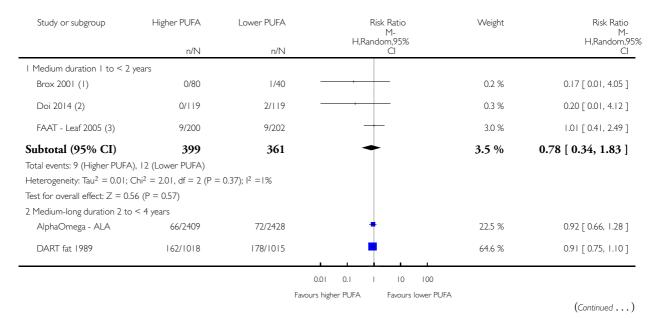
- (I) Fatal MI/ sudden death
- (2) Cardiac deaths
- (3) Fatal MI

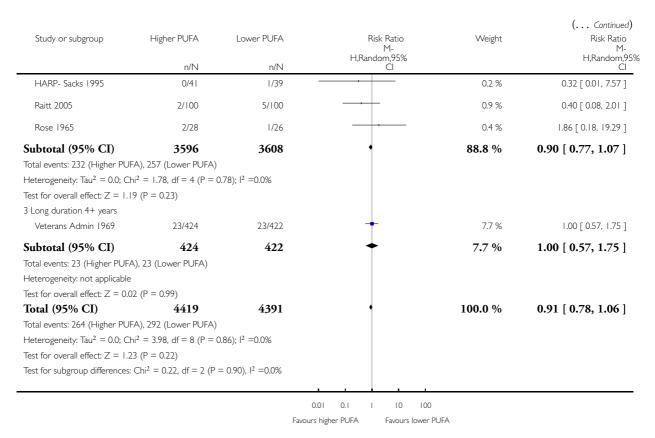
Analysis 2.29. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 29 CHD mortality - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 29 CHD mortality - subgroup by duration





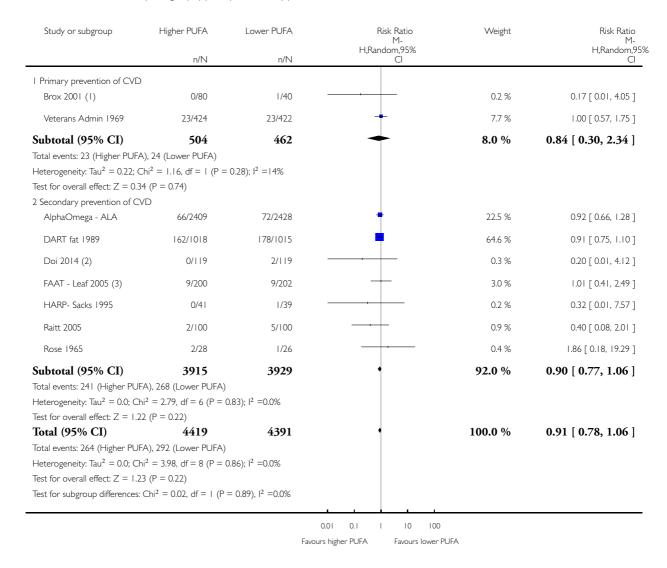
- (I) Fatal MI
- (2) Fatal MI/ sudden death
- (3) Cardiac deaths

Analysis 2.30. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 30 CHD mortality - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 30 CHD mortality - subgroup by primary or secondary prevention



⁽I) Fatal MI

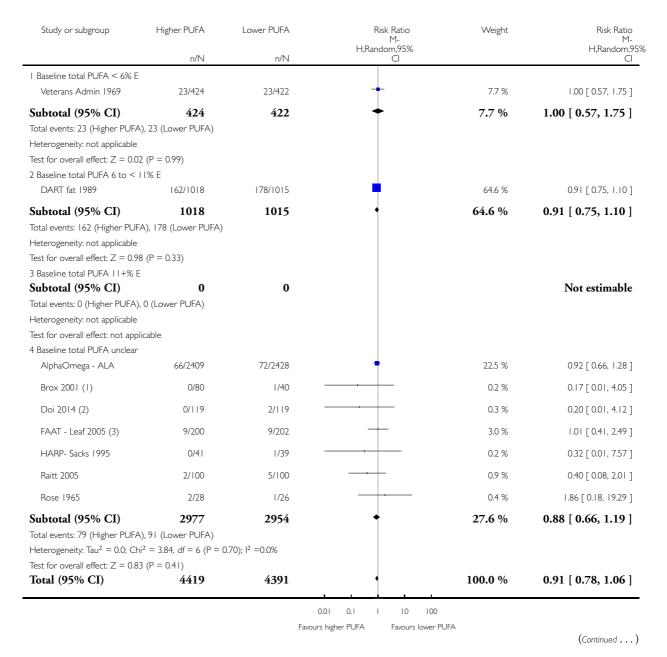
⁽²⁾ Fatal MI/ sudden death

⁽³⁾ Cardiac deaths

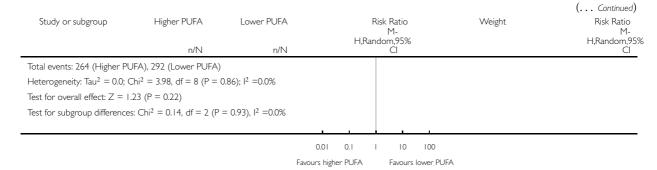
Analysis 2.31. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 31 CHD mortality - subgroup by baseline PUFA dose.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 31 CHD mortality - subgroup by baseline PUFA dose



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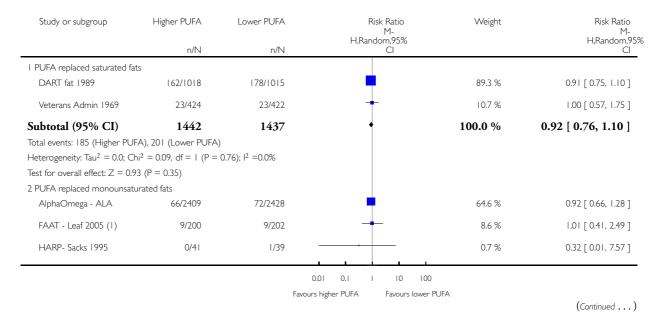
- (I) Fatal MI
- (2) Fatal MI/ sudden death
- (3) Cardiac deaths

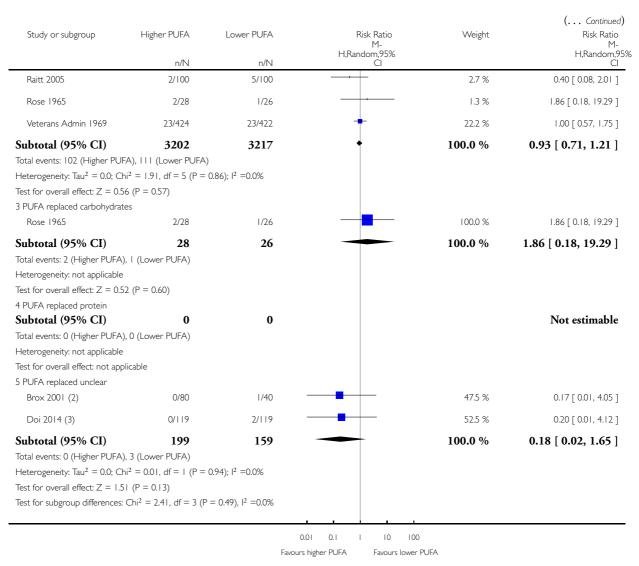
Analysis 2.32. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 32 CHD mortality - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 32 CHD mortality - subgroup by replacement





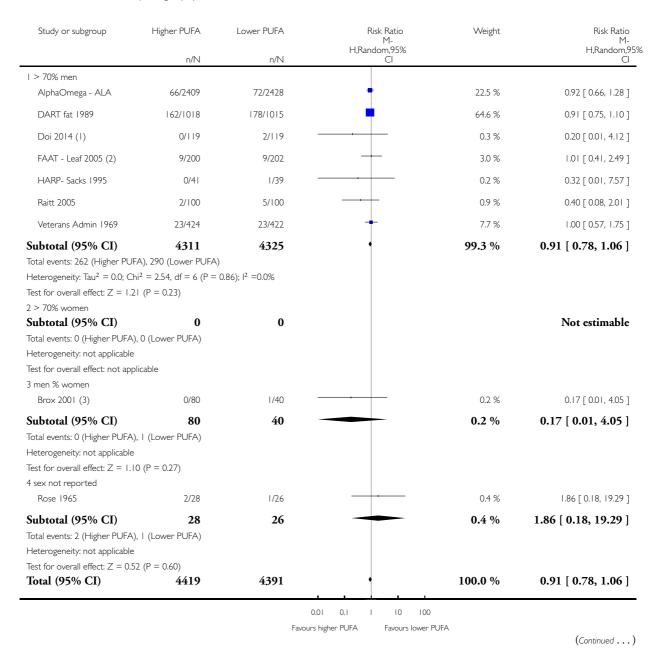
- (I) Cardiac deaths
- (2) Fatal MI
- (3) Fatal MI/ sudden death

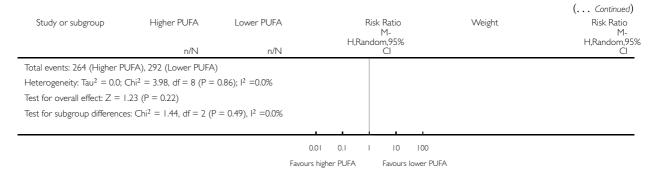
Analysis 2.33. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 33 CHD mortality - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 33 CHD mortality - subgroup by sex





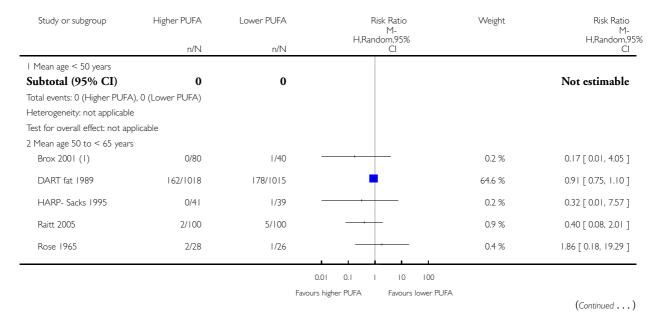
- (I) Fatal MI/ sudden death
- (2) Cardiac deaths
- (3) Fatal MI

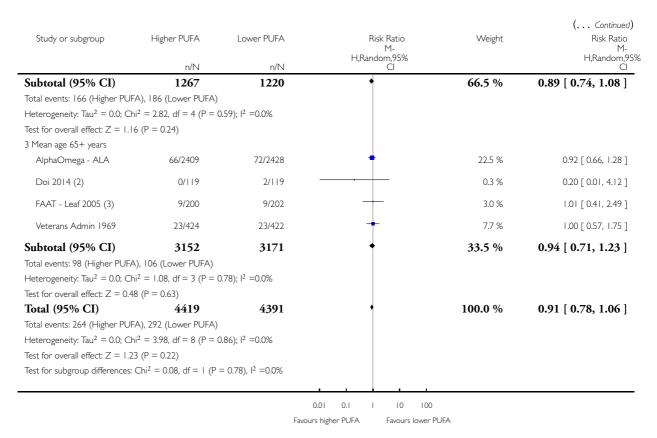
Analysis 2.34. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 34 CHD mortality - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 34 CHD mortality - subgroup by age





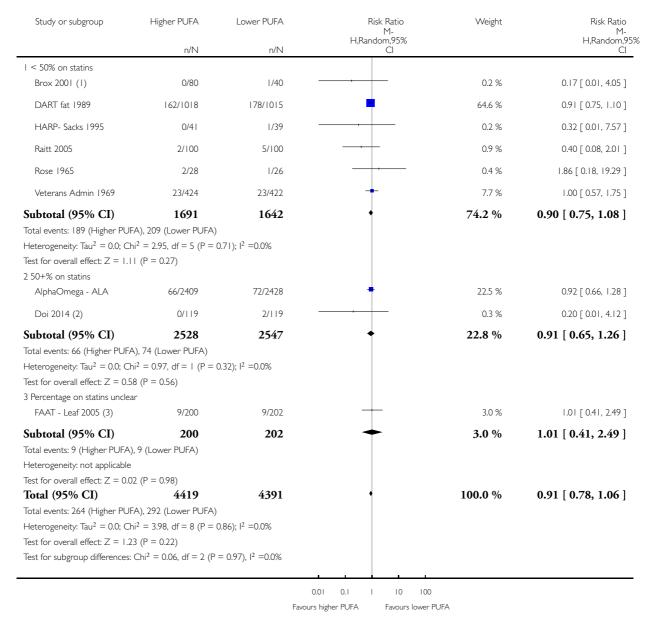
- (I) Fatal MI
- (2) Fatal MI/ sudden death
- (3) Cardiac deaths

Analysis 2.35. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 35 CHD mortality - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 35 CHD mortality - subgroup by statin use



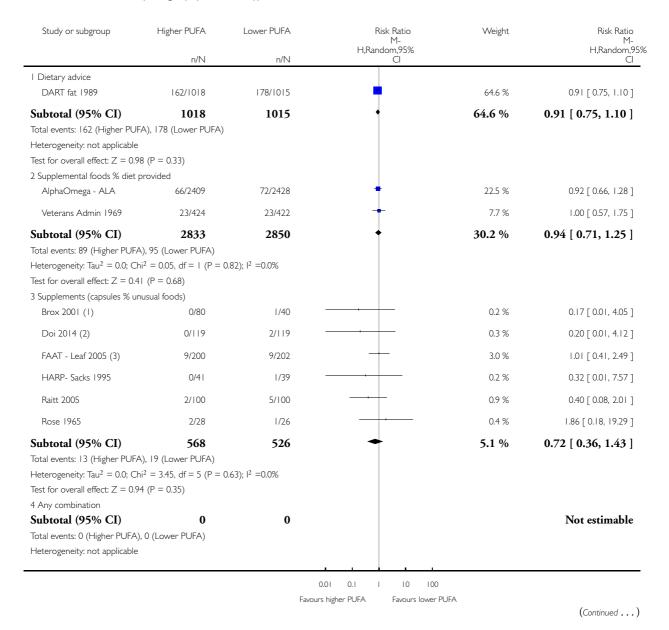
- (I) Fatal MI
- (2) Fatal MI/ sudden death
- (3) Cardiac deaths

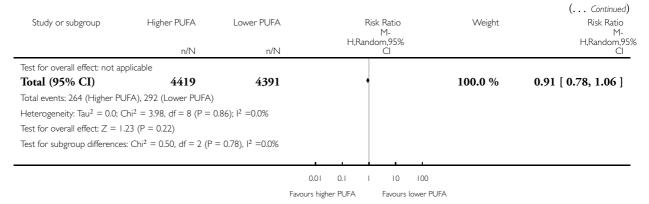
Analysis 2.36. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 36 CHD mortality - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 36 CHD mortality - subgroup by intervention type





(I) Fatal MI

(2) Fatal MI/ sudden death

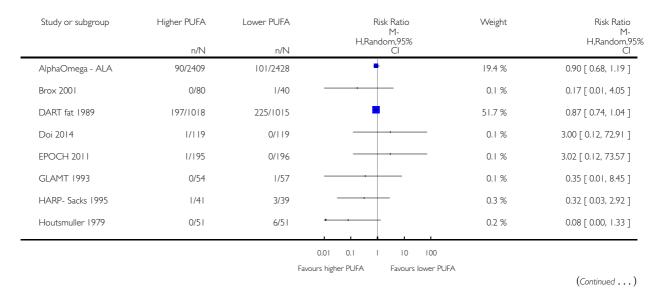
(3) Cardiac deaths

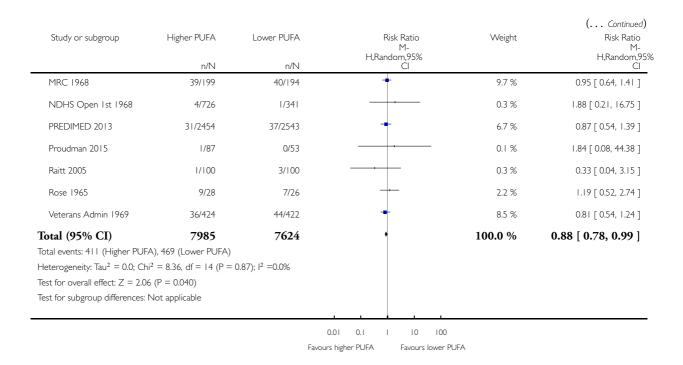
Analysis 2.37. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 37 MYOCARDIAL INFARCTION (MI) - fatal and non fatal.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 37 MYOCARDIAL INFARCTION (MI) - fatal and non fatal



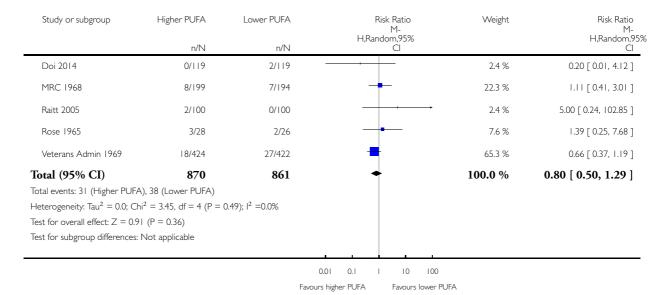


Analysis 2.38. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 38 SUDDEN CARDIAC DEATH (SCD).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 38 SUDDEN CARDIAC DEATH (SCD)

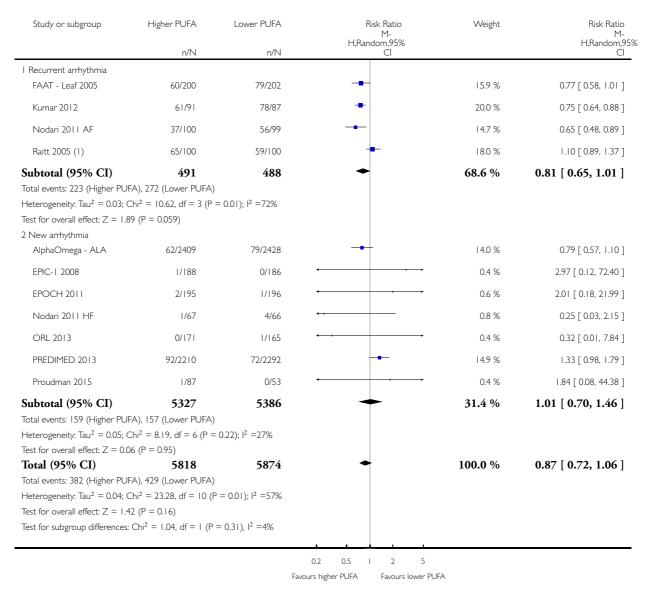


Analysis 2.39. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 39 ATRIAL FIBRILLATION (AF) & ARRHYTHMIAS (including AF, ventricular tachycardia (VT), ventricular fibrillation(VF).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

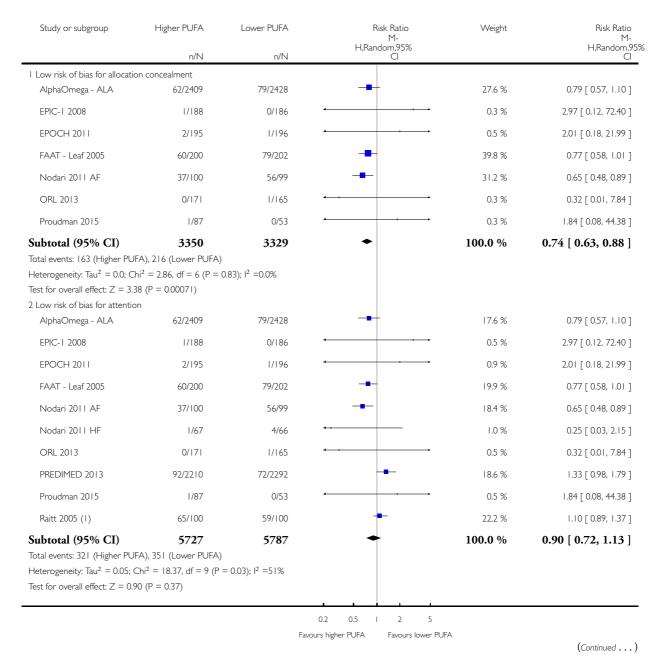
Outcome: 39 ATRIAL FIBRILLATION (AF) % ARRHYTHMIAS (including AF, ventricular tachycardia (VT), ventricular fibrillation(VF)

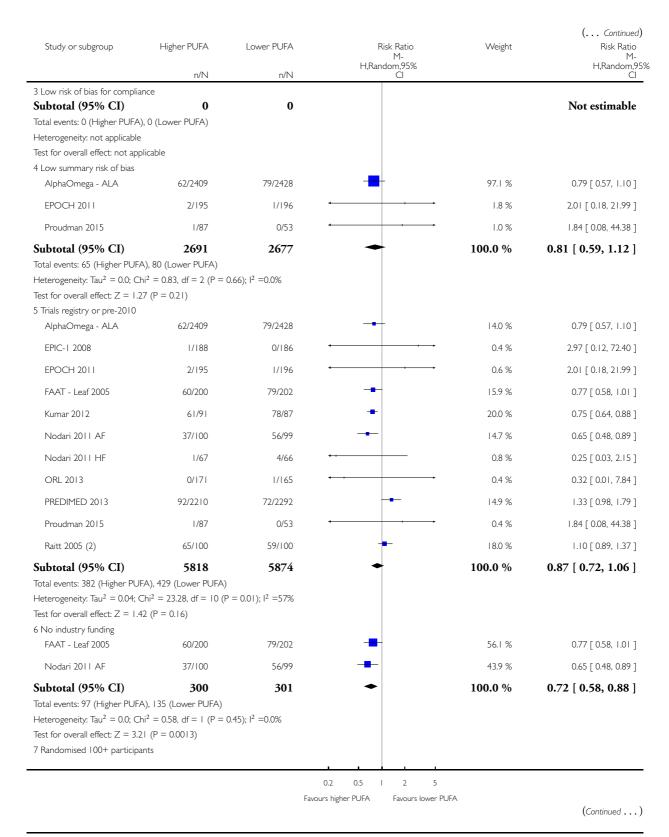


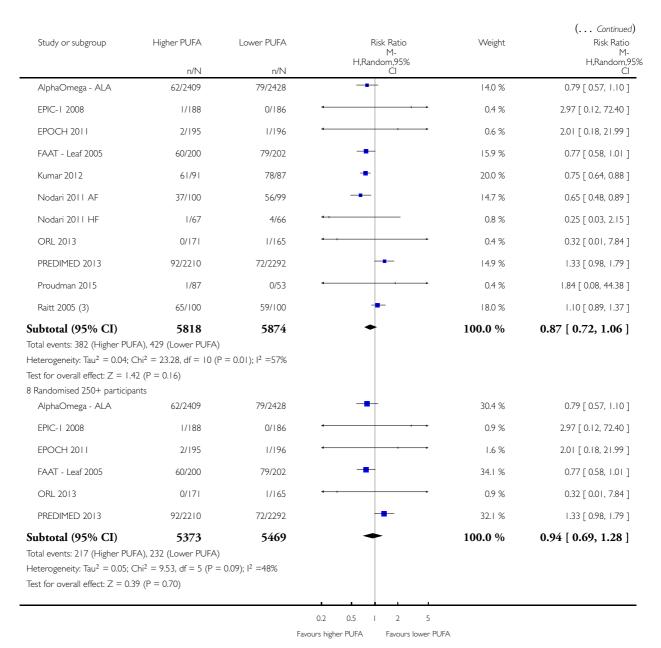
Analysis 2.40. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 40 AF - SA.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 40 AF - SA







⁽I) ICD therapy for VT/VF

⁽²⁾ ICD therapy for VT/VF

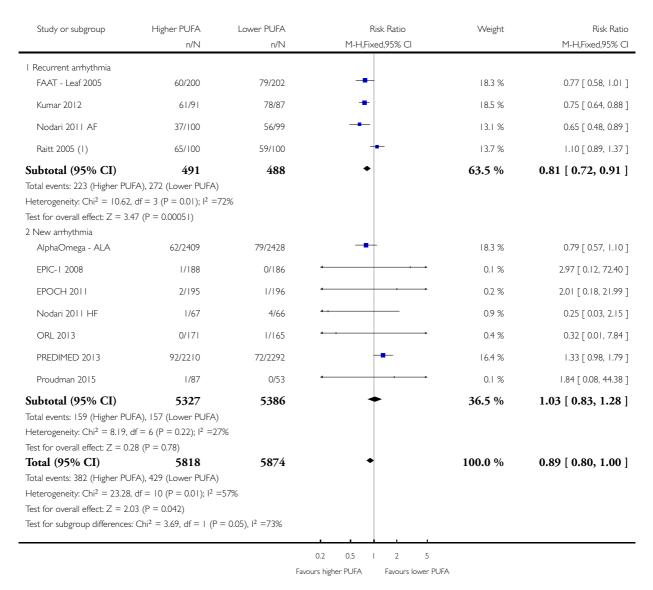
⁽³⁾ ICD therapy for VT/VF

Analysis 2.41. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 41 AF - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

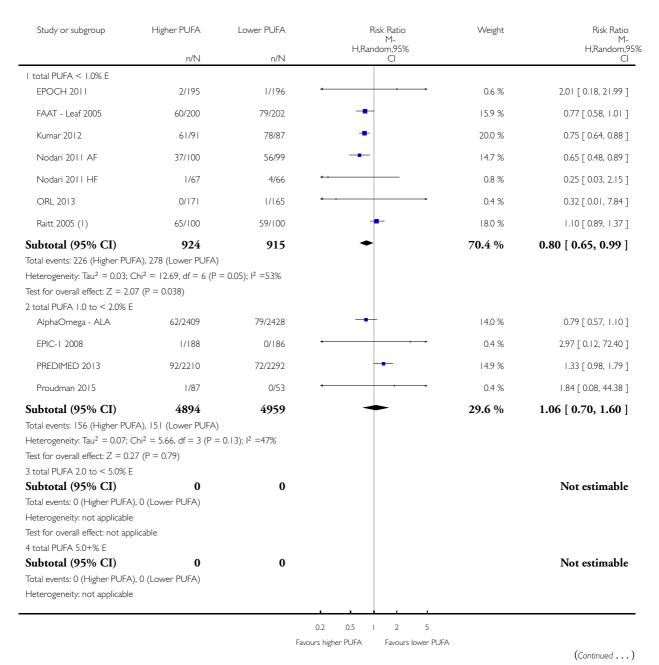
Outcome: 41 AF - SA fixed-effect

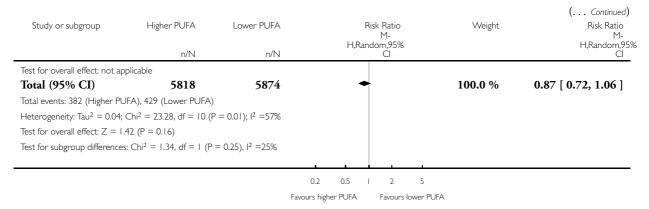


Analysis 2.42. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 42 AF - subgroup by PUFA dose.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 42 AF - subgroup by PUFA dose



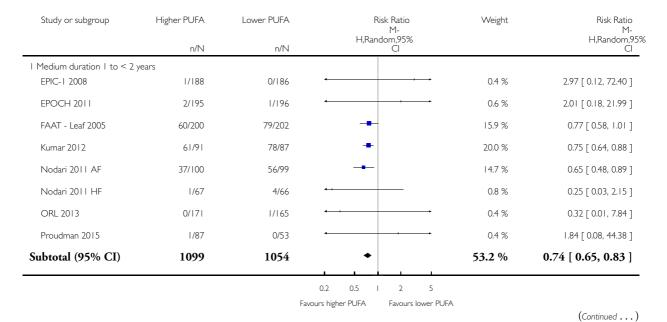


Analysis 2.43. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 43 AF - subgroup by duration.

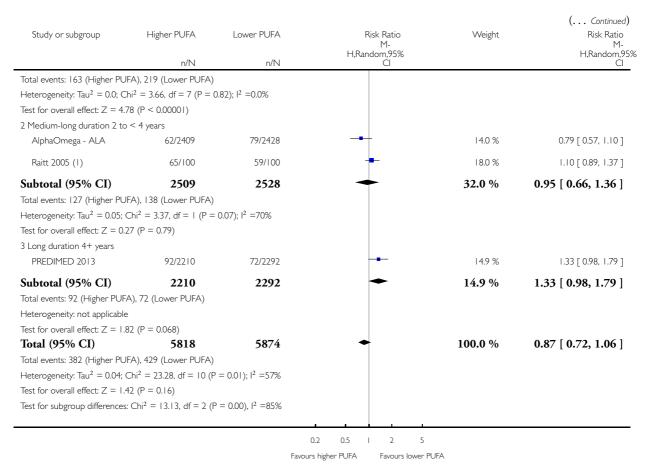
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 43 AF - subgroup by duration



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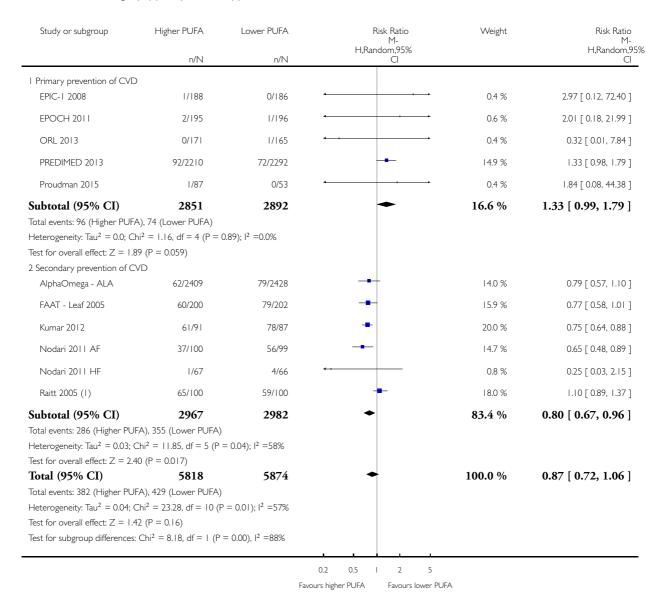


Analysis 2.44. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 44 AF - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

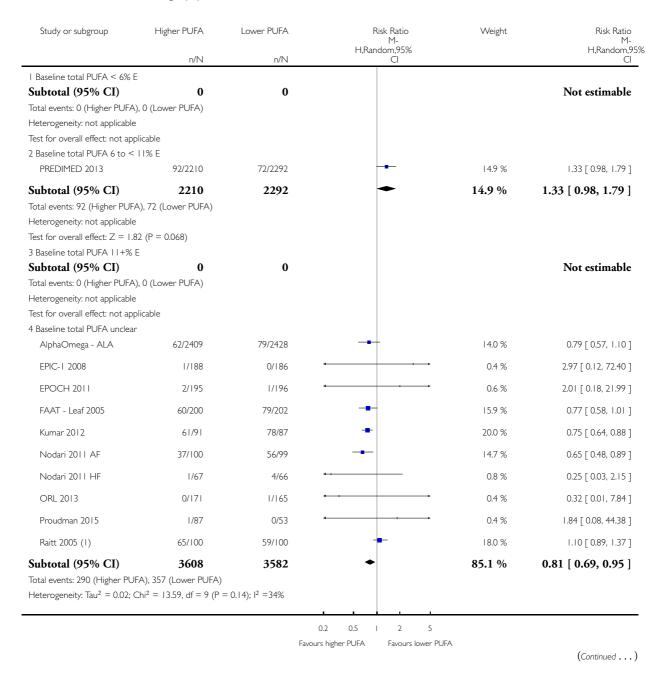
Outcome: 44 AF - subgroup by primary or secondary prevention

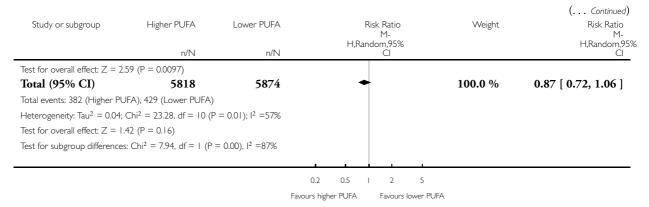


Analysis 2.45. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 45 Atrial fibrillation - subgroup by baseline PUFA dose.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 45 Atrial fibrillation - subgroup by baseline PUFA dose



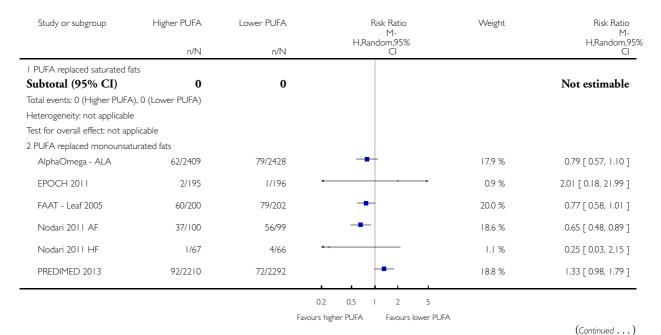


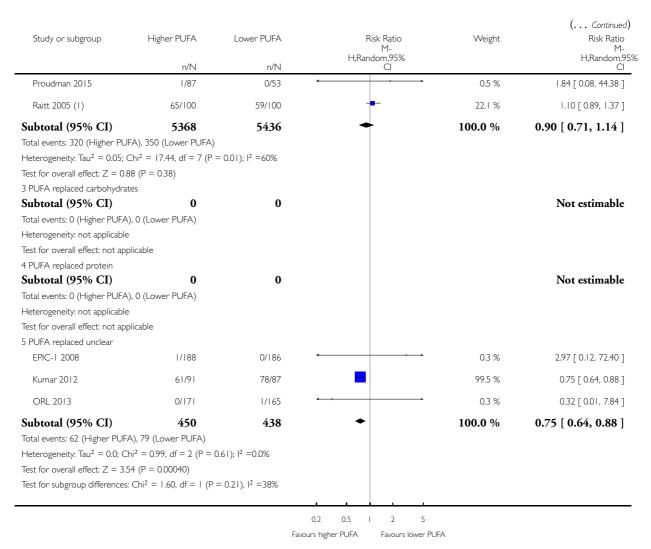
Analysis 2.46. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 46 AF - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 46 AF - subgroup by replacement

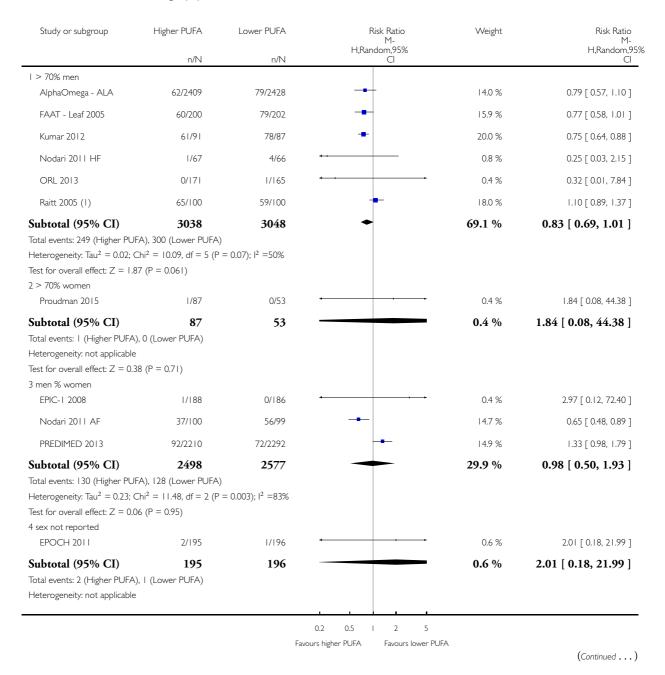


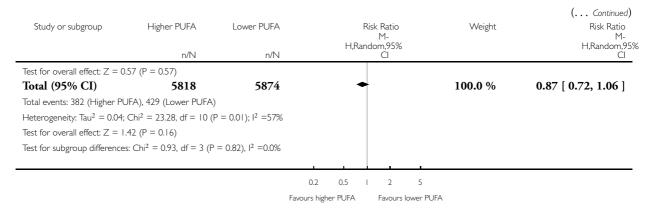


Analysis 2.47. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 47 Atrial fibrillation - subgroup by sex.

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 47 Atrial fibrillation - subgroup by sex



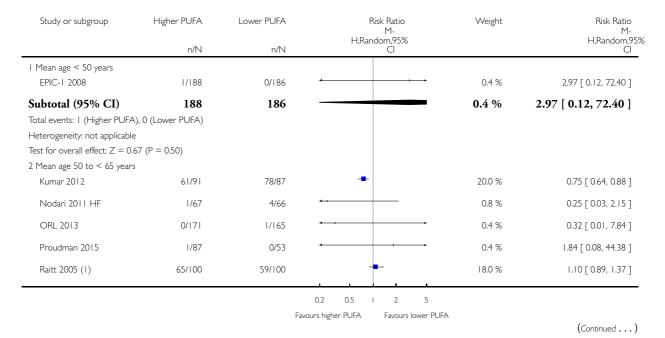


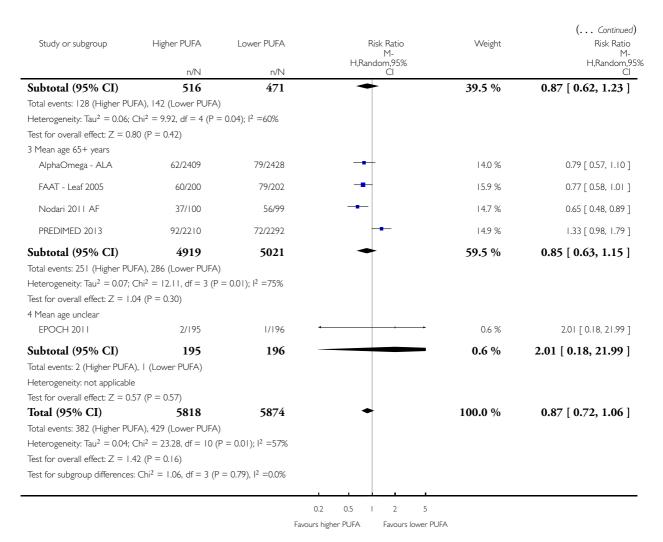
Analysis 2.48. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 48 AF - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 48 AF - subgroup by age



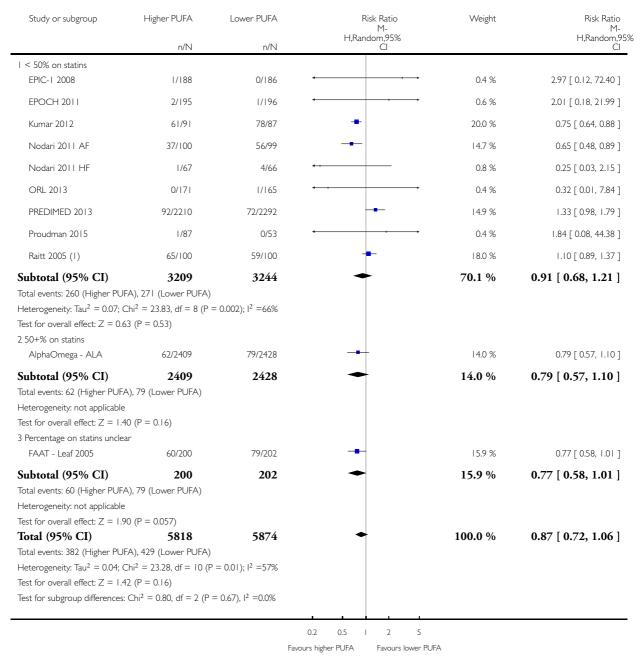


Analysis 2.49. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 49 AF - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 49 AF - subgroup by statin use



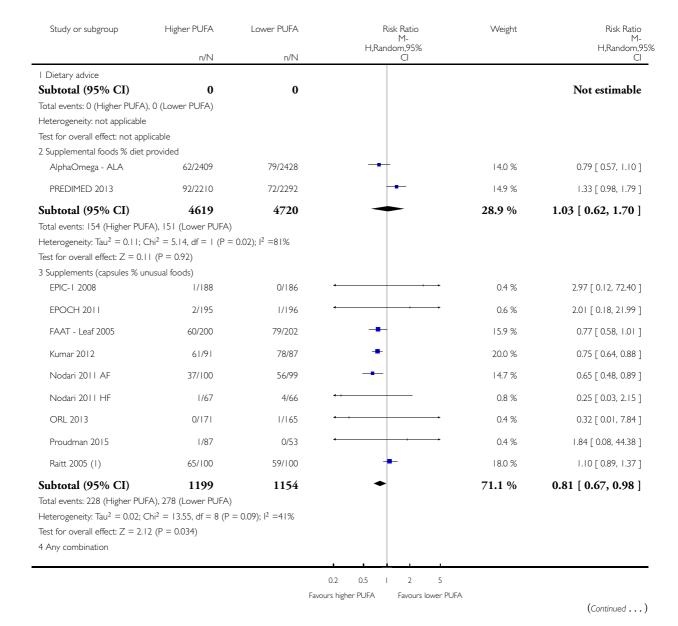
(1) ICD therapy for VT/VF

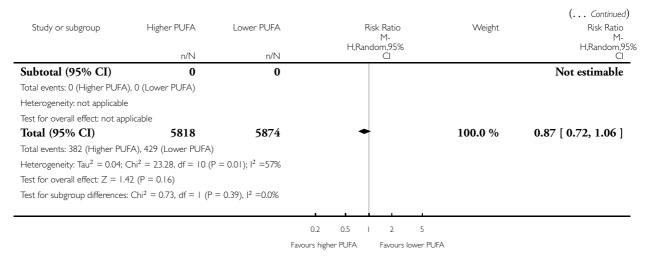
Analysis 2.50. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 50 AF - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 50 AF - subgroup by intervention type





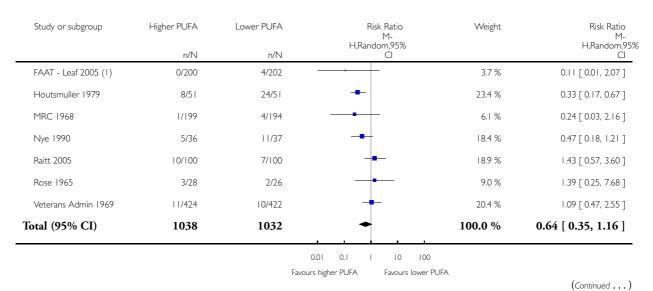
(I) ICD therapy for VT/VF

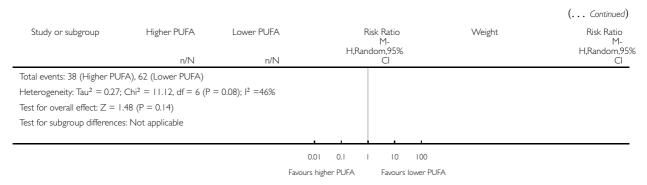
Analysis 2.51. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 51 ANGINA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 51 ANGINA





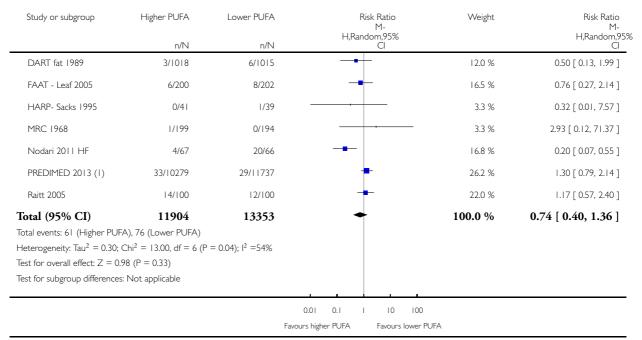
(I) Worsening angina

Analysis 2.52. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 52 HEART FAILURE.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 52 HEART FAILURE

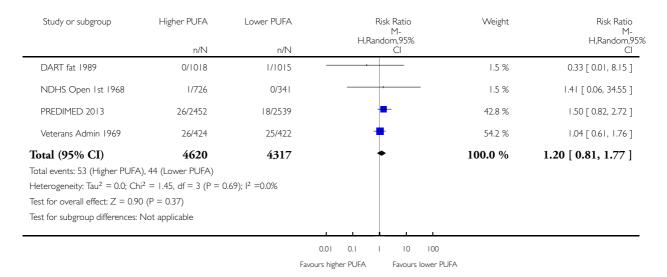


Analysis 2.53. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 53 PERIPHERAL ARTERIAL DISEASE (PAD).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 53 PERIPHERAL ARTERIAL DISEASE (PAD)

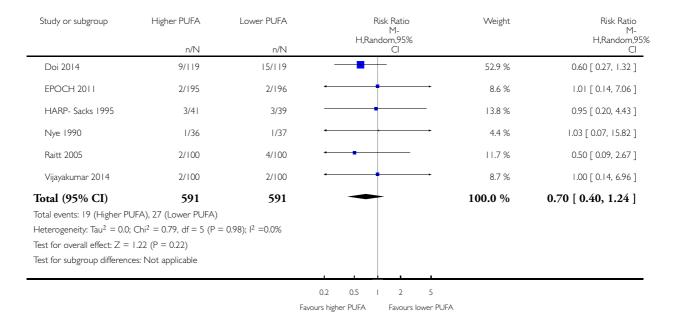


Analysis 2.54. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 54 REVASCULARISATION - angioplasty and/or coronary artery bypass grafting.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 54 REVASCULARISATION - angioplasty and/or coronary artery bypass grafting

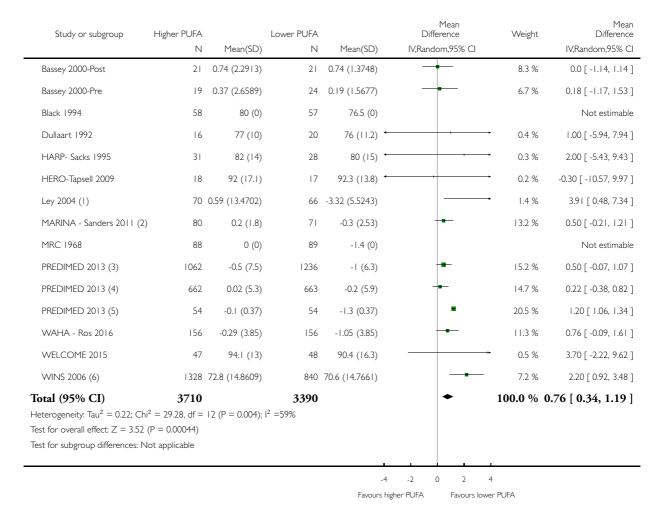


Analysis 3.1. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome I ADIPOSITY - BODY WEIGHT, kg.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: I ADIPOSITY - BODY WEIGHT, kg



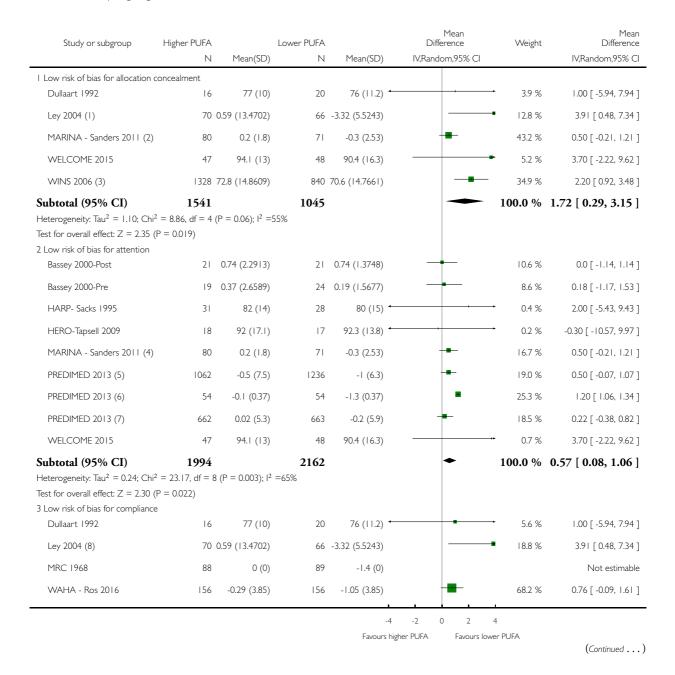
- (1) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (4) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (5) Barcelona hospital cohort at 5 years, Casa 2016
- (6) One year data

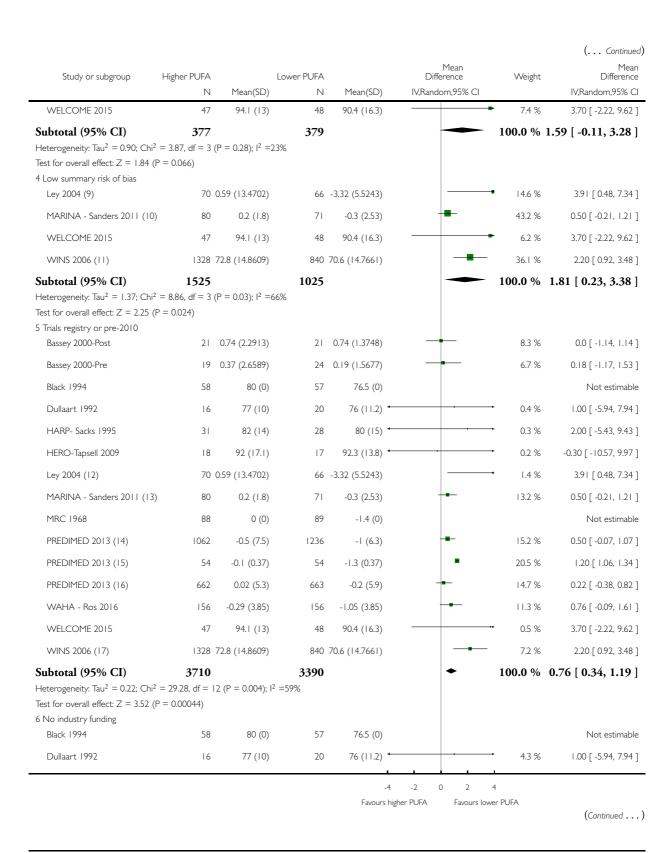
Analysis 3.2. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 2

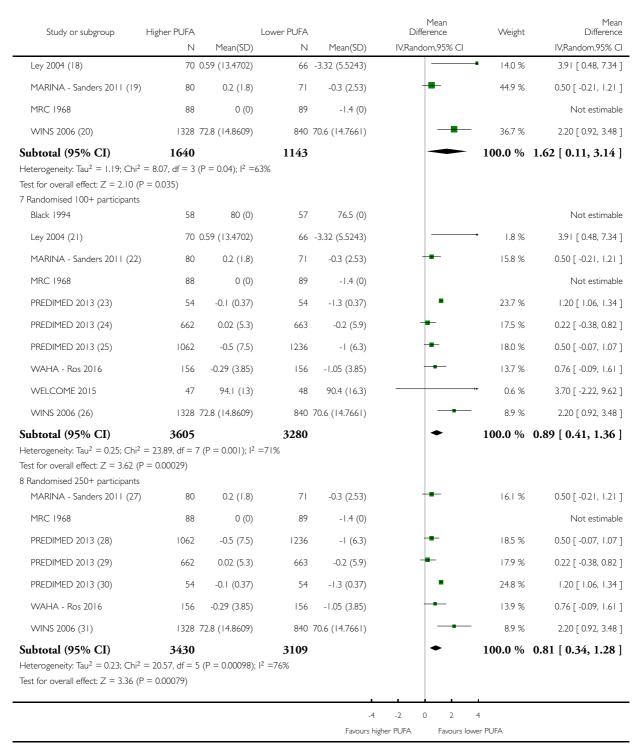
Body weight, kg - SA.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 2 Body weight, kg - SA







- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) One year data
- (4) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (5) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (6) Barcelona hospital cohort at 5 years, Casa 2016
- (7) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (8) Change data, variance presented as SDs, but assumed to be SEs and converted
- (9) Change data, variance presented as SDs, but assumed to be SEs and converted
- (10) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (II) One year data
- (12) Change data, variance presented as SDs, but assumed to be SEs and converted $\,$
- (13) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (14) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (15) Barcelona hospital cohort at 5 years, Casa 2016
- (16) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (17) One year data
- (18) Change data, variance presented as SDs, but assumed to be SEs and converted
- (19) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (20) One year data
- (21) Change data, variance presented as SDs, but assumed to be SEs and converted
- (22) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (23) Barcelona hospital cohort at 5 years, Casa 2016
- (24) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (25) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (26) One year data
- (27) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (28) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (29) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (30) Barcelona hospital cohort at 5 years, Casa 2016
- (31) One year data

Analysis 3.3. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 3 Body weight, kg - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 3 Body weight, kg - SA fixed-effect

Mear Difference IV,Fixed,95% C	Weight	Mean Difference /,Fixed,95% CI	IV	Mean(SD)	Lower PUFA	Mean(SD)	Higher PUFA	Study or subgroup
0.0 [-1.14, 1.14	1.2 %			0.74 (1.3748)	21	0.74 (2.2913)	21	Bassey 2000-Post
0.18 [-1.17, 1.53	0.9 %			0.19 (1.5677)	24	0.37 (2.6589)	19	Bassey 2000-Pre
Not estimable				76.5 (0)	57	80 (0)	58	Black 1994
1.00 [-5.94, 7.94	0.0 %			76 (11.2)	20	77 (10)	16	Dullaart 1992
2.00 [-5.43, 9.43	0.0 %			80 (15)	28	82 (14)	31	HARP- Sacks 1995
-0.30 [-10.57, 9.97	0.0 %			92.3 (13.8)	17	92 (17.1)	18	HERO-Tapsell 2009
3.91 [0.48, 7.34	0.1 %			-3.32 (5.5243)	66	0.59 (13.4702)	70	Ley 2004 (I)
0.50 [-0.21, 1.21	3.2 %	-		-0.3 (2.53)	71	0.2 (1.8)	80	MARINA - Sanders 2011 (2)
Not estimable				-1.4 (0)	89	0 (0)	88	MRC 1968
0.50 [-0.07, 1.07	4.9 %	 		-1 (6.3)	1236	-0.5 (7.5)	1062	PREDIMED 2013 (3)
0.22 [-0.38, 0.82	4.4 %	+-		-0.2 (5.9)	663	0.02 (5.3)	662	PREDIMED 2013 (4)
1.20 [1.06, 1.34	82.0 %	•		-1.3 (0.37)	54	-0.1 (0.37)	54	PREDIMED 2013 (5)
0.76 [-0.09, 1.61	2.2 %	-		-1.05 (3.85)	156	-0.29 (3.85)	156	WAHA - Ros 2016
3.70 [-2.22, 9.62	0.0 %		_	90.4 (16.3)	48	94.1 (13)	47	WELCOME 2015
2.20 [0.92, 3.48	1.0 %			70.6 (14.7661)	840	72.8 (14.8609)	1328	WINS 2006 (6)
1.08 [0.96, 1.21]	100.0 %	•			3390	4); I ² =59%	`	Cotal (95% CI) Just the contract of the cotal (95% CI) Just the cotal
							(. 0.0000.)	est for subgroup differences: N

⁽I) Change data, variance presented as SDs, but assumed to be SEs and converted $\,$

^{(2) 0.9}g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

⁽³⁾ Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

⁽⁴⁾ Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

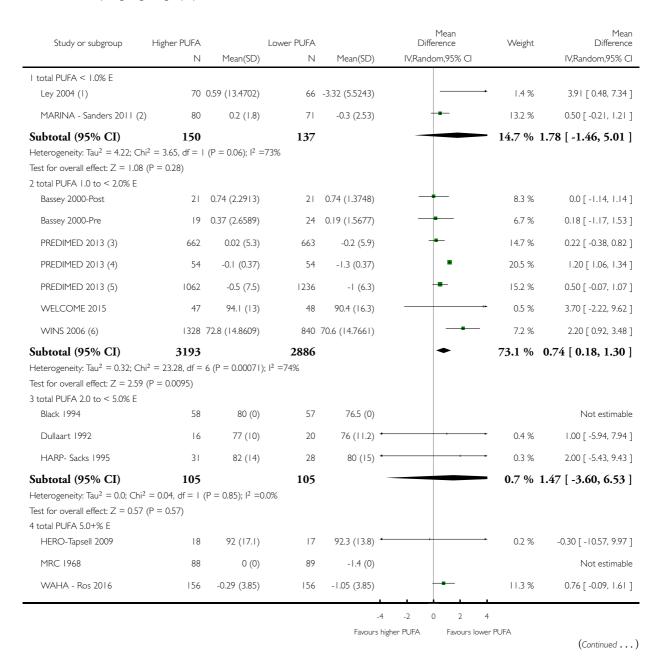
⁽⁵⁾ Barcelona hospital cohort at 5 years, Casa 2016

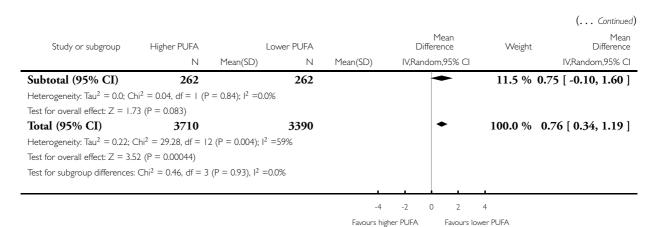
⁽⁶⁾ One year data

Analysis 3.4. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 4
Body weight, kg - subgroup by PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 4 Body weight, kg - subgroup by PUFA dose





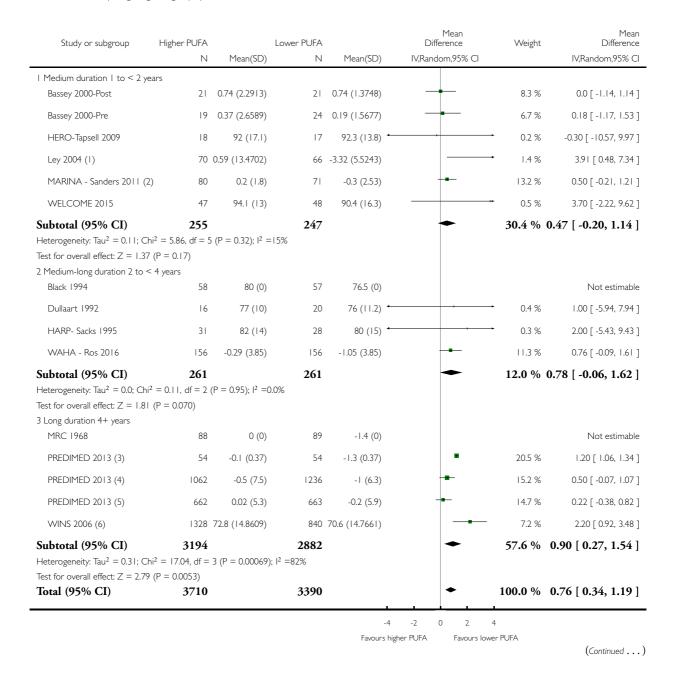
- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (6) One year data

Analysis 3.5. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 5

Body weight, kg - subgroup by duration.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 5 Body weight, kg - subgroup by duration



(... Continued)

Study or subgroup	Higher PUFA	Lower f	PUFA		D	Mean ifference	٧	Veight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rar	ndom,95% C	I		IV,Random,95% CI
Heterogeneity: Tau ² = 0.22; ($Chi^2 = 29.28, df = 12$	$2 (P = 0.004); I^2 = 59\%$							
Test for overall effect: $Z = 3.5$	52 (P = 0.00044)								
Test for subgroup differences	: $Chi^2 = 0.87$, $df = 2$	$(P = 0.65), I^2 = 0.0\%$							
				-4	-2	0 2	4		
				Favours high	ner PUFA	Favours	lower PUFA		

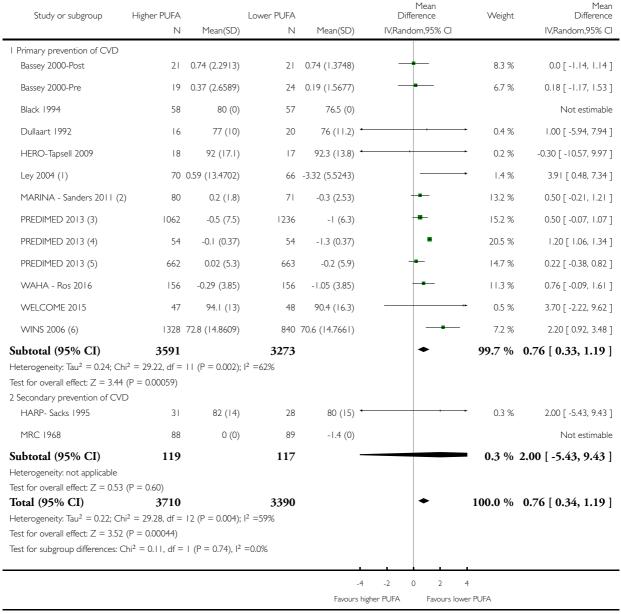
- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (6) One year data

Analysis 3.6. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 6 Body weight, kg - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 6 Body weight, kg - subgroup by primary or secondary prevention

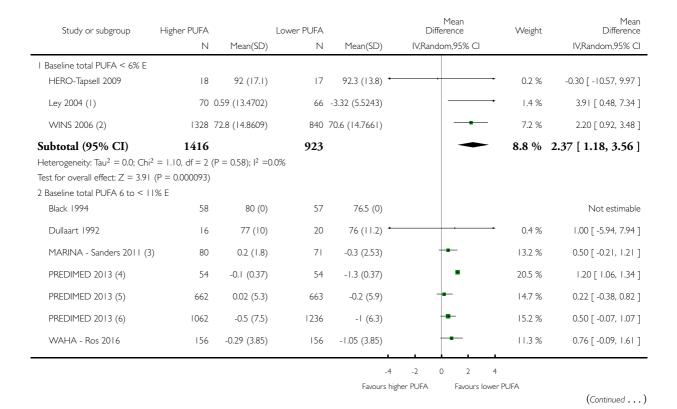


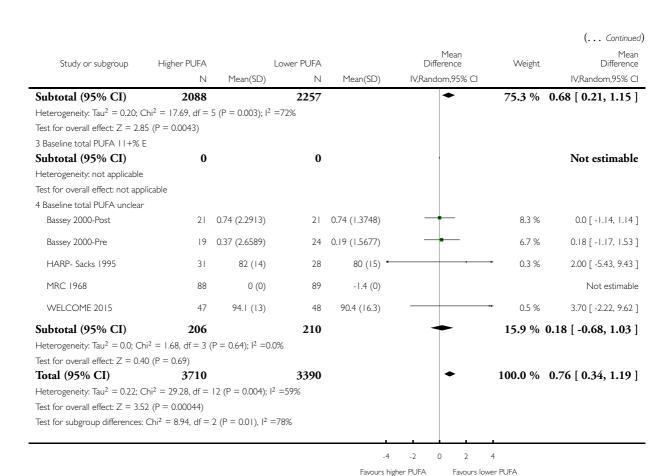
- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (6) One year data

Analysis 3.7. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 7
Body weight, kg - subgroup by baseline PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 7 Body weight, kg - subgroup by baseline PUFA dose



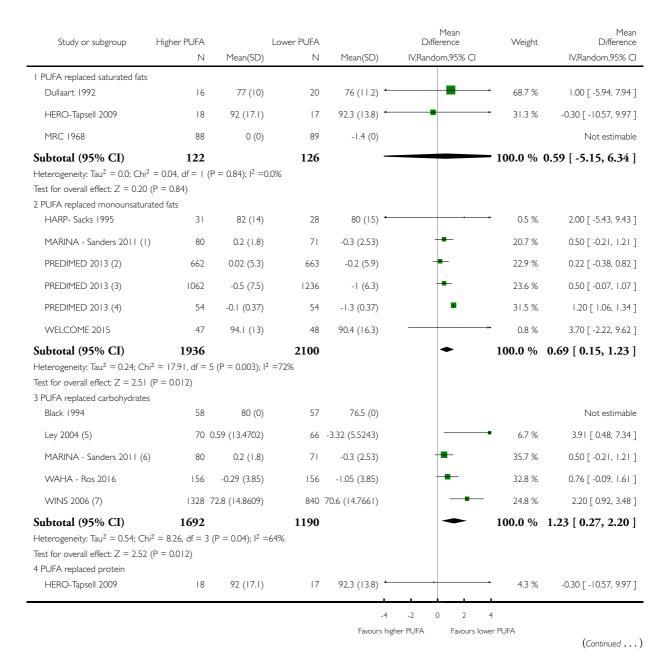


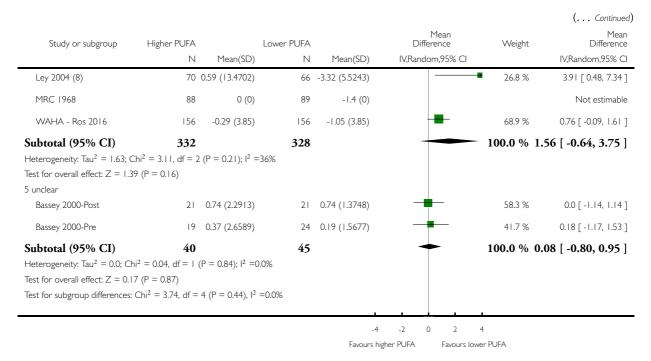
- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) One year data
- (3) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (6) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data

Analysis 3.8. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 8 Body weight, kg - subgroup by replacement.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 8 Body weight, kg - subgroup by replacement





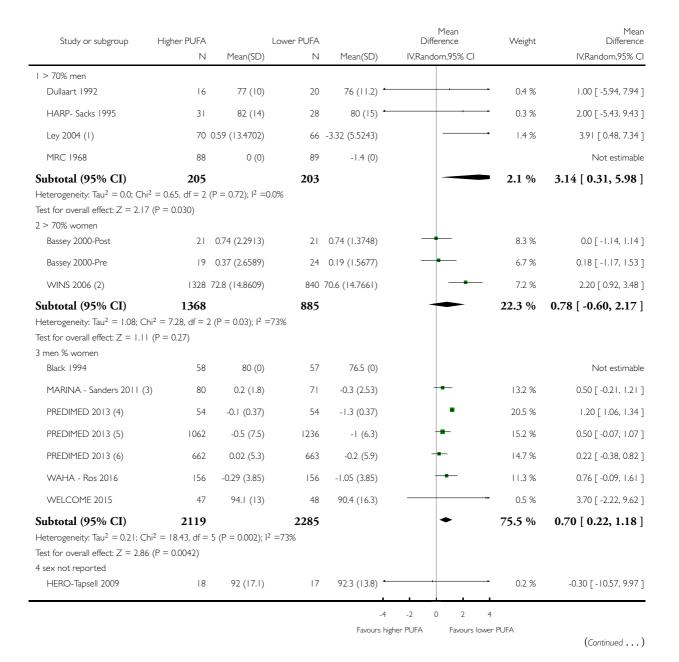
- (1) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (2) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (3) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Change data, variance presented as SDs, but assumed to be SEs and converted
- (6) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (7) One year data
- (8) Change data, variance presented as SDs, but assumed to be SEs and converted

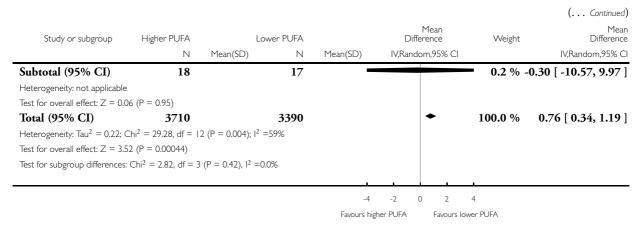
Analysis 3.9. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 9

Body weight, kg - subgroup by sex.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 9 Body weight, kg - subgroup by sex



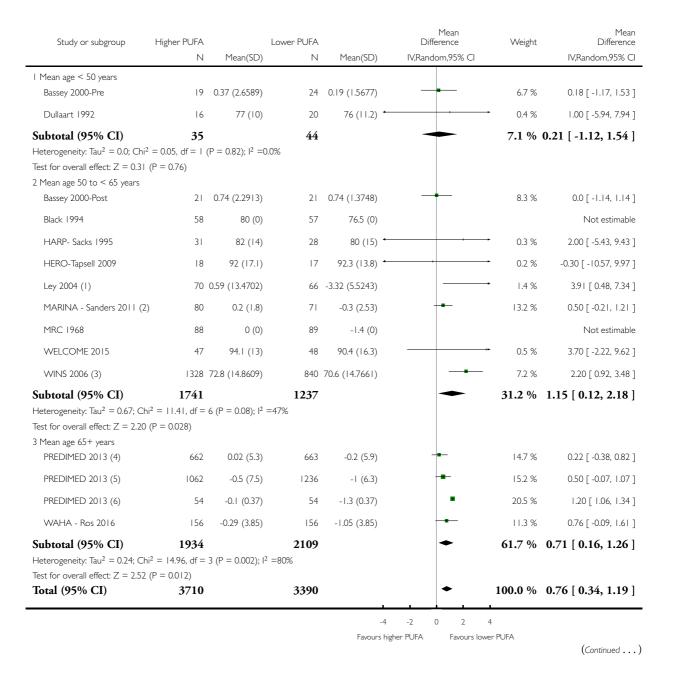


- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) One year data
- (3) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (6) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

Analysis 3.10. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 10 Body weight, kg - subgroup by age.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 10 Body weight, kg - subgroup by age



(... Continued)

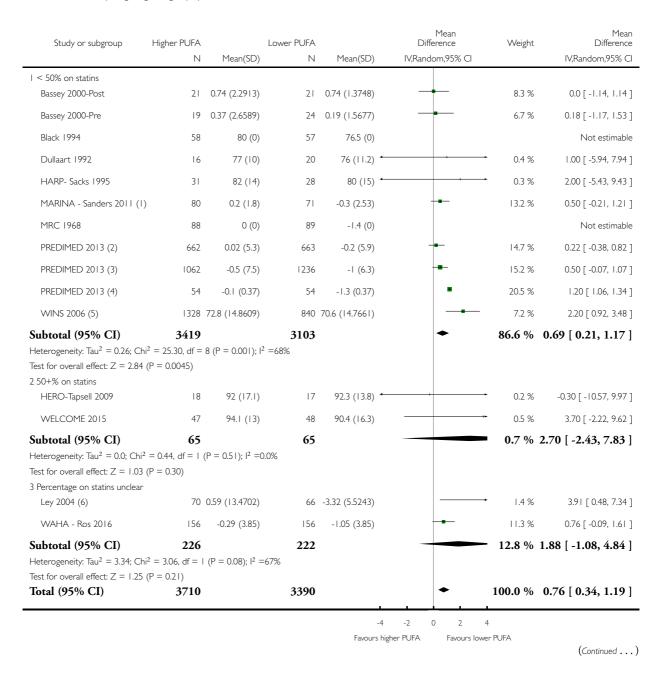
Study or subgroup	Higher PUFA	Lowe	r PUFA		Di	Mean ifference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Ran	idom,95% CI		IV,Random,95% CI
Heterogeneity: Tau ² = 0.22; ($Chi^2 = 29.28, df = 12$	$2 (P = 0.004); I^2 = 59$	%					
Test for overall effect: $Z = 3.5$	52 (P = 0.00044)							
Test for subgroup differences	$Chi^2 = 1.25, df = 2$	(P = 0.54), $I^2 = 0.0\%$						
							1.	
				-4	-2	0 2	4	
				Favours high	ner PUFA	Favours Id	ower PUFA	

- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) One year data
- (4) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (5) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (6) Barcelona hospital cohort at 5 years, Casa 2016

Analysis 3.11. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 11 Body weight, kg - subgroup by statin use.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: II Body weight, kg - subgroup by statin use



(... Continued)

Study or subgroup	Higher PUFA	Lowe	r PUFA		Dir	Mean fference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Ran	dom,95% CI		IV,Random,95% CI
Heterogeneity: Tau ² = 0.22; ($Chi^2 = 29.28, df = 12$	$2 (P = 0.004); I^2 = 59$	%					
Test for overall effect: $Z = 3.5$	52 (P = 0.00044)							
Test for subgroup differences:	: $Chi^2 = 1.17$, $df = 2$	$(P = 0.56), I^2 = 0.0\%$						
				-4	-2	0 2	4	
				Favours high	ner PUFA	Favours Io	ower PUFA	

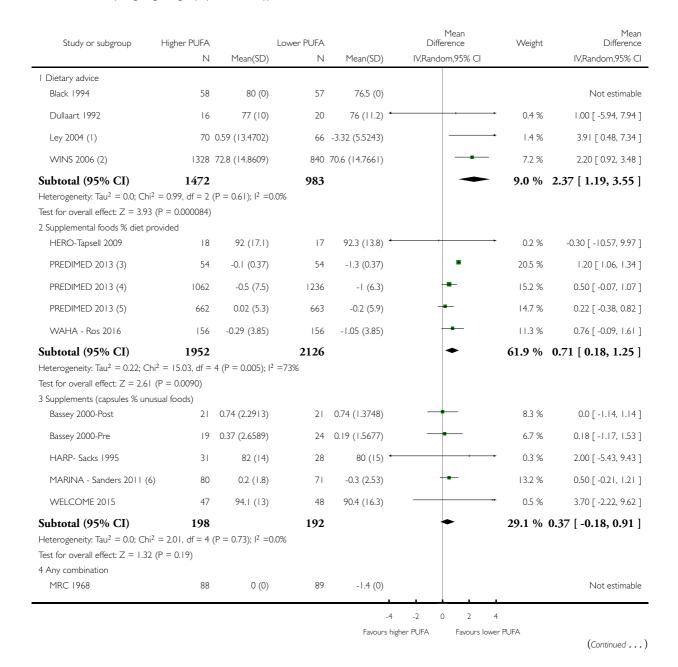
- (1) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (2) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (3) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) One year data
- (6) Change data, variance presented as SDs, but assumed to be SEs and converted

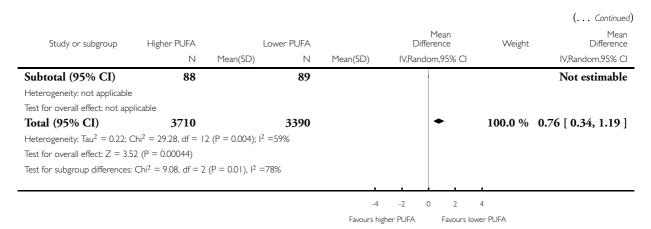
Analysis 3.12. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 12

Body weight, kg - subgroup by intervention type.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 12 Body weight, kg - subgroup by intervention type





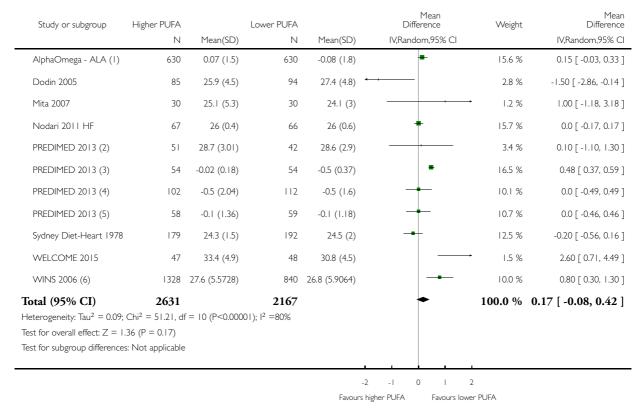
- (I) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) One year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (6) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

Analysis 3.13. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 13 ADIPOSITY - Body Mass Index (BMI), kg/m2.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 13 ADIPOSITY - Body Mass Index (BMI), kg/m2

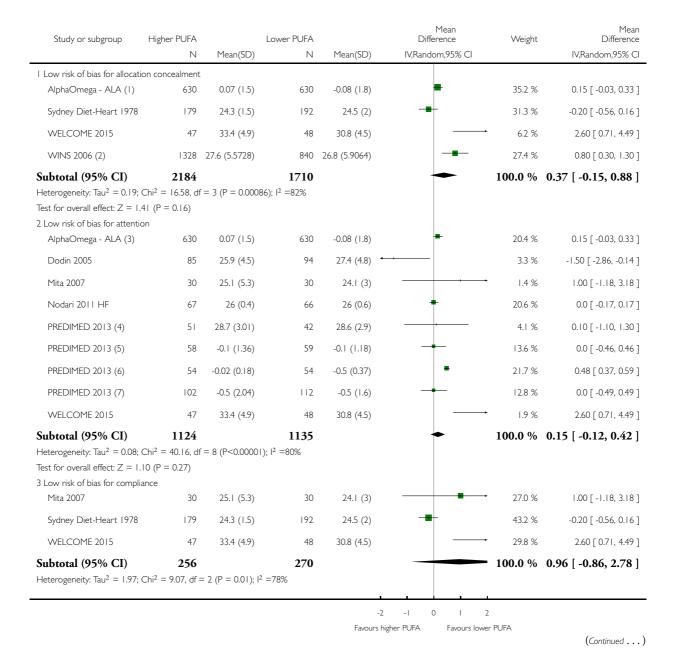


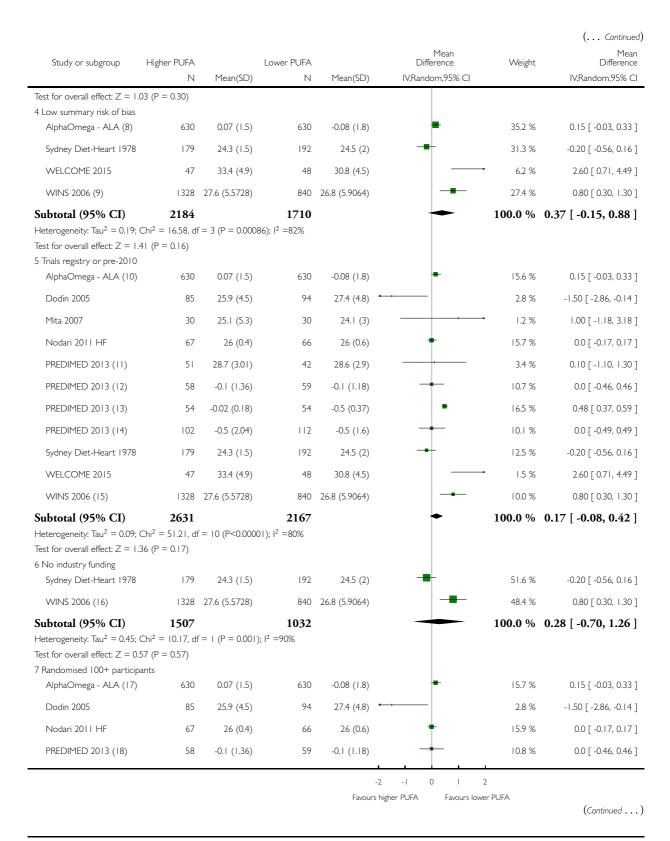
- (1) Numer of participants equally divided between groups
- (2) Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) One year data

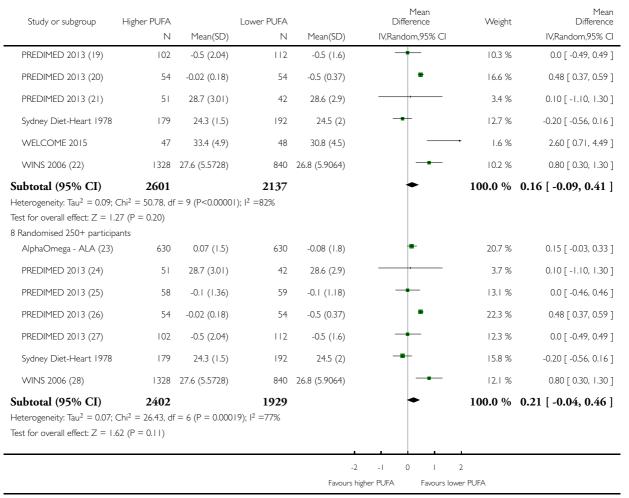
Analysis 3.14. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 14 BMI, kg/m2 - SA.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 14 BMI, kg/m2 - SA







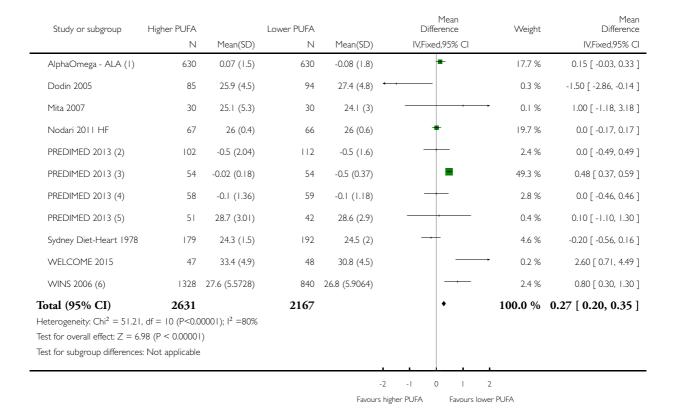
- (I) Numer of participants equally divided between groups
- (2) One year data
- (3) Numer of participants equally divided between groups
- (4) Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Barcelona hospital cohort at 5 years, Casa 2016
- (7) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (8) Numer of participants equally divided between groups
- (9) One year data
- (10) Numer of participants equally divided between groups
- (11) Reus subcohort, 2 year data
- (12) Damasceno 2013, Barcelona North subcohort, I year data
- (13) Barcelona hospital cohort at 5 years, Casa 2016
- (14) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (15) One year data
- (16) One year data
- (17) Numer of participants equally divided between groups
- (18) Damasceno 2013, Barcelona North subcohort, I year data
- (19) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (20) Barcelona hospital cohort at 5 years, Casa 2016
- (21) Reus subcohort, 2 year data
- (22) One year data
- (23) Numer of participants equally divided between groups
- (24) Reus subcohort, 2 year data
- (25) Damasceno 2013, Barcelona North subcohort, I year data
- (26) Barcelona hospital cohort at 5 years, Casa 2016
- (27) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (28) One year data

Analysis 3.15. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 15 BMI, kg/m2 - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 15 BMI, kg/m2 - SA fixed-effect



⁽I) Numer of participants equally divided between groups

⁽²⁾ Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

⁽³⁾ Barcelona hospital cohort at 5 years, Casa 2016

⁽⁴⁾ Damasceno 2013, Barcelona North subcohort, I year data

⁽⁵⁾ Reus subcohort, 2 year data

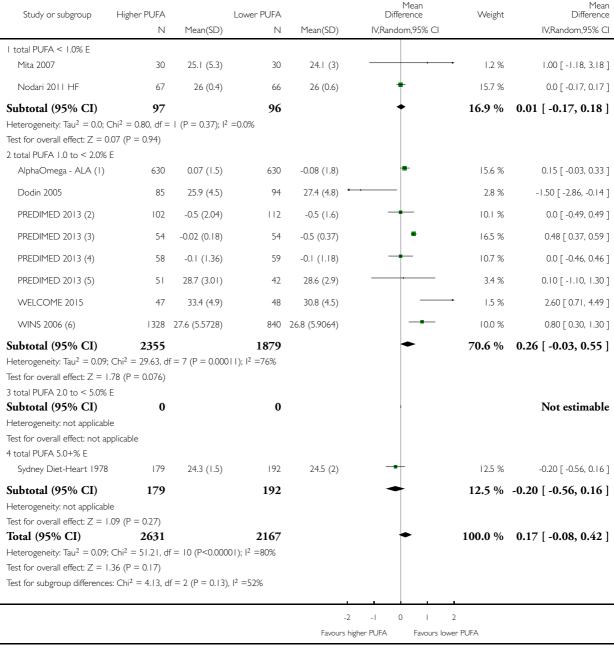
⁽⁶⁾ One year data

Analysis 3.16. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 16 BMI, kg/m2 - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 16 BMI, kg/m2 - subgroup by PUFA dose



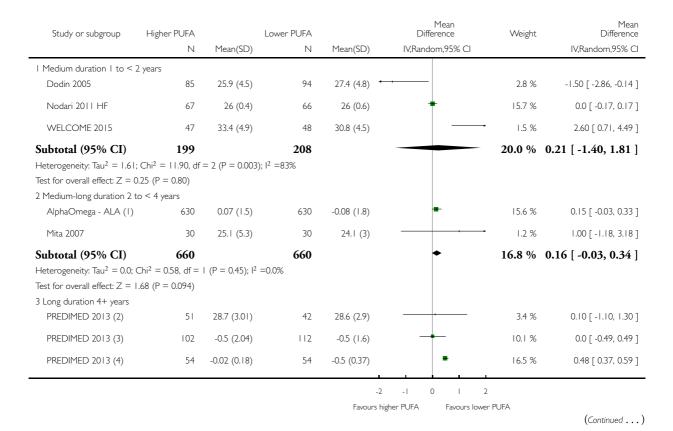
- (I) Numer of participants equally divided between groups
- (2) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Reus subcohort, 2 year data
- (6) One year data

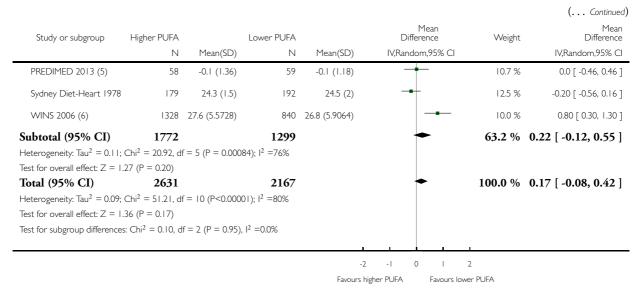
Analysis 3.17. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 17 BMI, kg/m2 - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 17 BMI, kg/m2 - subgroup by duration





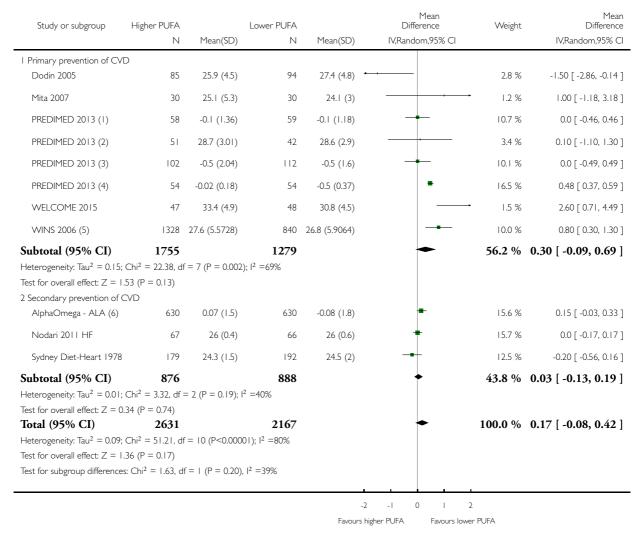
- (I) Numer of participants equally divided between groups
- (2) Reus subcohort, 2 year data
- (3) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) One year data

Analysis 3.18. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 18 BMI, kg/m2 - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 18 BMI, kg/m2 - subgroup by primary or secondary prevention

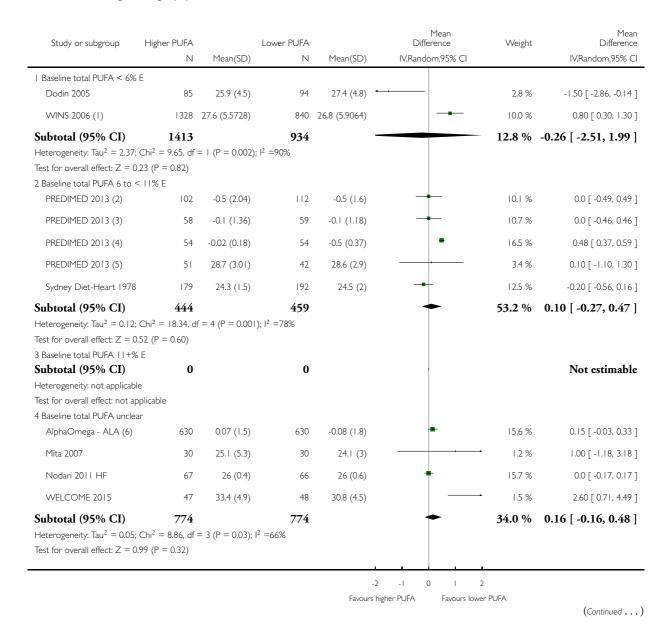


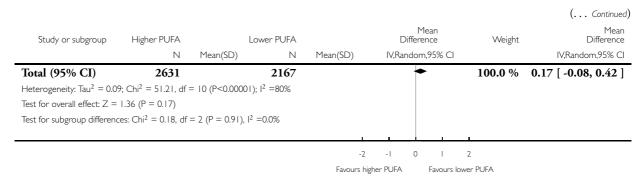
- (I) Damasceno 2013, Barcelona North subcohort, I year data
- (2) Reus subcohort, 2 year data
- (3) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) One year data
- (6) Numer of participants equally divided between groups

Analysis 3.19. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 19 BMI, kg/m2 - subgroup by baseline PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 19 BMI, kg/m2 - subgroup by baseline PUFA dose





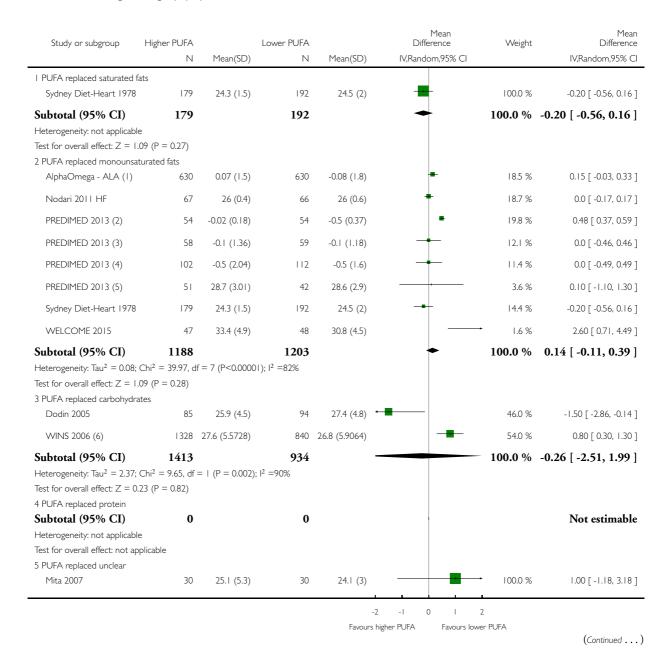
- (I) One year data
- (2) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Reus subcohort, 2 year data
- (6) Numer of participants equally divided between groups

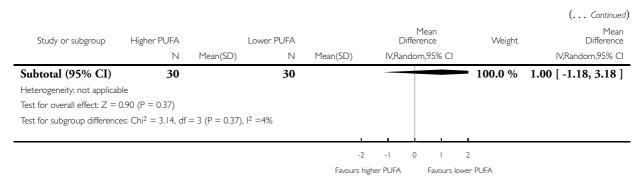
Analysis 3.20. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 20 BMI, kg/m2 - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 20 BMI, kg/m2 - subgroup by replacement





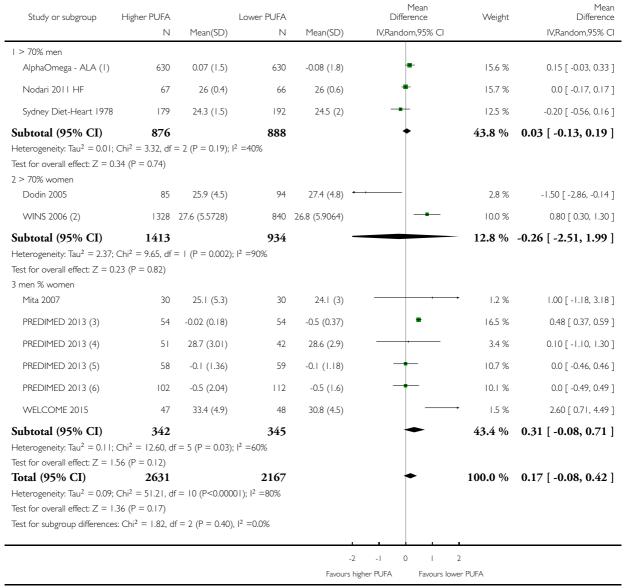
- (I) Numer of participants equally divided between groups
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (5) Reus subcohort, 2 year data
- (6) One year data

Analysis 3.21. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 21 BMI, kg/m2 - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 21 BMI, kg/m2 - subgroup by sex



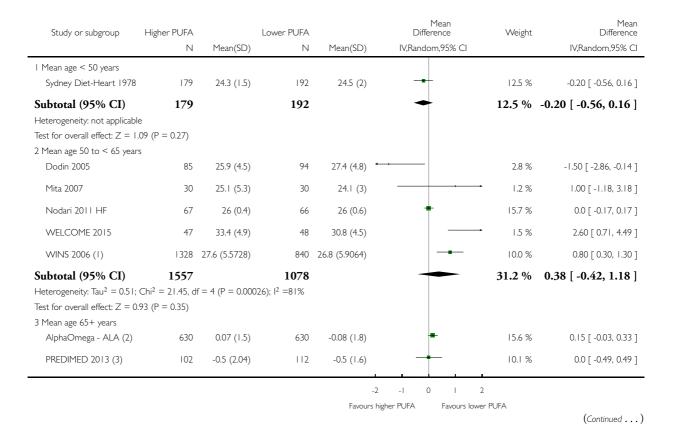
- (I) Numer of participants equally divided between groups
- (2) One year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

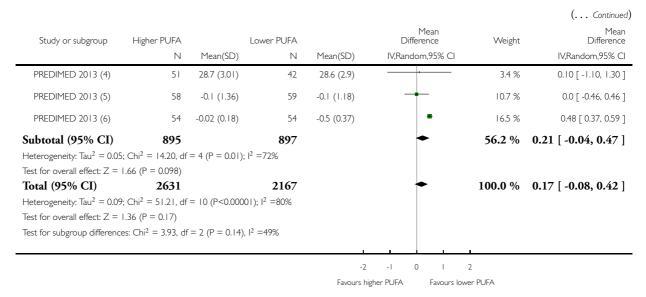
Analysis 3.22. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 22 BMI, kg/m2 - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 22 BMI, kg/m2 - subgroup by age





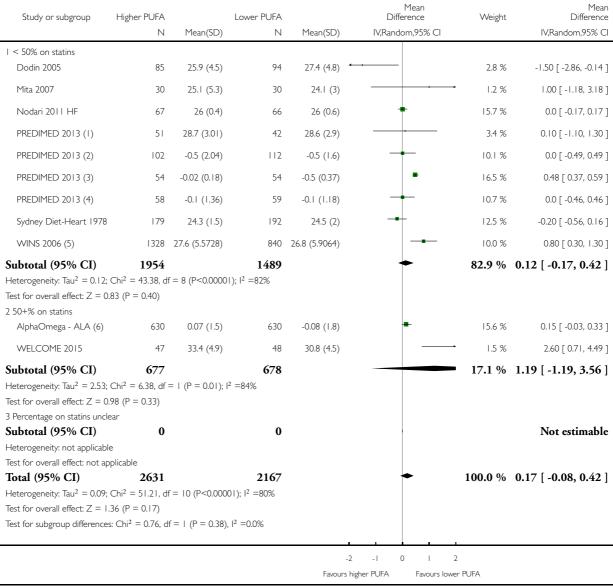
- (I) One year data
- (2) Numer of participants equally divided between groups
- (3) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (4) Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Barcelona hospital cohort at 5 years, Casa 2016

Analysis 3.23. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 23 BMI, kg/m2 - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 23 BMI, kg/m2 - subgroup by statin use



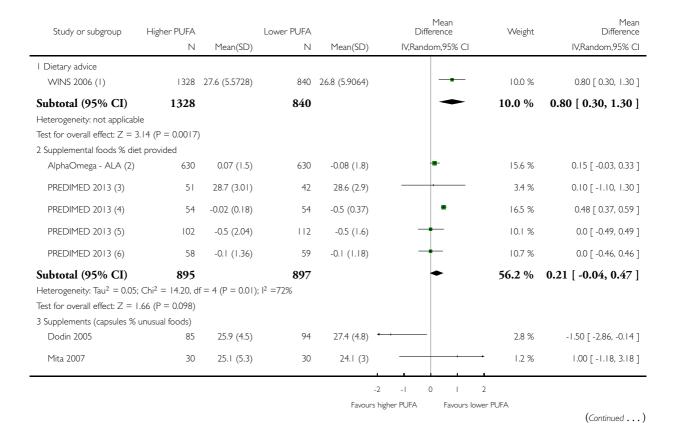
- (I) Reus subcohort, 2 year data
- (2) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) One year data
- (6) Numer of participants equally divided between groups

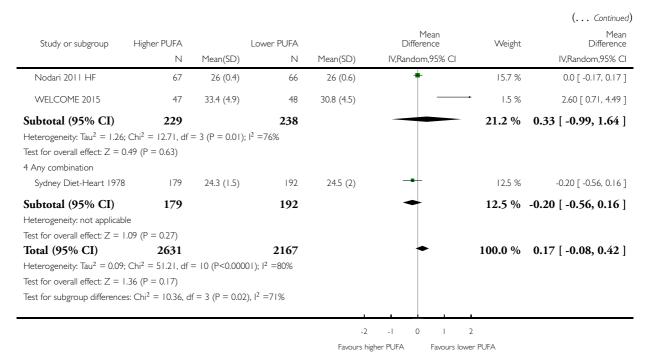
Analysis 3.24. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 24 BMI, kg/m2 - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 24 BMI, kg/m2 - subgroup by intervention type





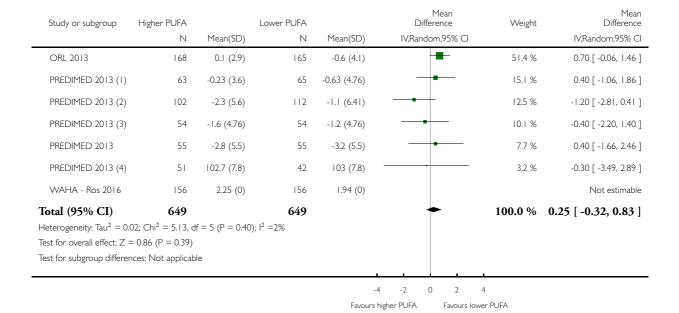
- (I) One year data
- (2) Numer of participants equally divided between groups
- (3) Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (6) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.25. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 25 Adiposity - waist circumference, cm.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 25 Adiposity - waist circumference, cm



⁽I) AP-UNAV centre, 3 year data

⁽²⁾ Canaries cohort, change to 1 year, Alvarez-Perez 2016

⁽³⁾ Barcelona hospital cohort at 5 years, Casa 2016

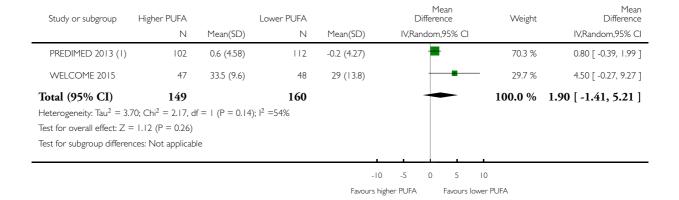
⁽⁴⁾ Reus subcohort, 2 year data

Analysis 3.26. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 26 Adiposity - % body fat.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 26 Adiposity - % body fat



(I) Canaries cohort, change to I year, Alvarez-Perez 2016

Analysis 3.27. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 27 Adiposity - body fat, kg.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 27 Adiposity - body fat, kg



Analysis 3.28. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 28 Serum TOTAL CHOLESTEROL (TC, mmoL/L).

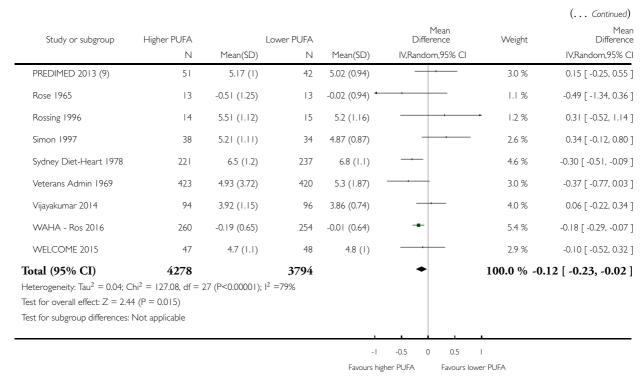
Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 28 Serum TOTAL CHOLESTEROL (TC, mmoL/L)

Mean Difference	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup	
IV,Random,95% CI		IV,Random,95% CI	Mean(SD)	Ν	Mean(SD)	N		
-0.15 [-0.47, 0.17]	3.6 %		3.75 (0.67)	36	3.6 (0.74)	38	Ahn 2016	
-0.02 [-0.13, 0.09]	5.4 %	+	-0.28 (0.98)	605	-0.3 (0.98)	605	AlphaOmega - ALA	
-0.01 [-0.33, 0.31]	3.6 %		7.9 (0.8)	37	7.8896 (0.8168)	67	Brox 2001 (I)	
-0.26 [-0.37, -0.15]	5.5 %	+	6.55 (1.1)	860	6.29 (1.13)	855	DART fat 1989	
0.12 [-0.14, 0.38]	4.2 %	+-	5.4 (0.79)	75	5.52 (0.9)	91	DIPP-Tokudome 2015 (2)	
-0.30 [-0.51, -0.09]	4.6 %		5.96 (0.72)	94	5.66 (0.72)	85	Dodin 2005	
0.03 [-0.38, 0.44]	3.0 %		4.99 (0.62)	28	5.02 (0.96)	31	HARP- Sacks 1995	
0.30 [-0.30, 0.90]	1.9 %		4.6 (1)	17	4.9 (0.8)	18	HERO-Tapsell 2009	
-0.47 [-0.76, -0.18]	3.9 %		6.9 (0.81)	48	6.43 (0.65)	48	Houtsmuller 1979	
0.10 [-0.28, 0.48]	3.2 %		0.15 (0.7312)	66	-0.05 (1.4223)	70	Ley 2004 (3)	
0.10 [-0.15, 0.35]	4.3 %		0.1 (0.63)	71	0.2 (0.8987)	80	MARINA - Sanders 2011 (4)	
0.16 [-0.18, 0.50]	3.5 %	+	-0.58 (0.7221)	28	-0.42 (0.5447)	26	Mendis 2001	
-0.12 [-0.58, 0.34]	2.6 %		5.27 (0.99)	30	5.15 (0.83)	30	Mita 2007	
Not estimable			-0.47 (0)	89	-1.11 (0)	88	MRC 1968	
-0.81 [-1.00, -0.62]	4.8 %	-	0.18 (0.5713) —	51	-0.9901 (0.6366)	141	NDHS Faribault 1968 (5)	
-0.42 [-0.50, -0.34]	5.6 %	•	0.25 (0.5274)	309	-0.6663 (0.693)	653	NDHS Open 1st 1968 (6)	
-0.10 [-0.31, 0.11]	4.6 %	-	4.9 (0.62)	66	4.8 (0.62)	67	Nodari 2011 HF	
0.63 [-0.30, 1.56]	1.0 %	- 	6.2 (1.31)	12	6.83 (I)	12	Nye 1990	
-0.05 [-0.37, 0.27]	3.6 %		-0.3 (0.89)	59	-0.35 (0.9)	58	PREDIMED 2013 (7)	
-0.21 [-0.57, 0.15]	3.3 %		-0.8 (0.99)	54	-1.01 (0.92)	54	PREDIMED 2013 (8)	

Favours higher PUFA Favours lower PUFA

(Continued . . .)

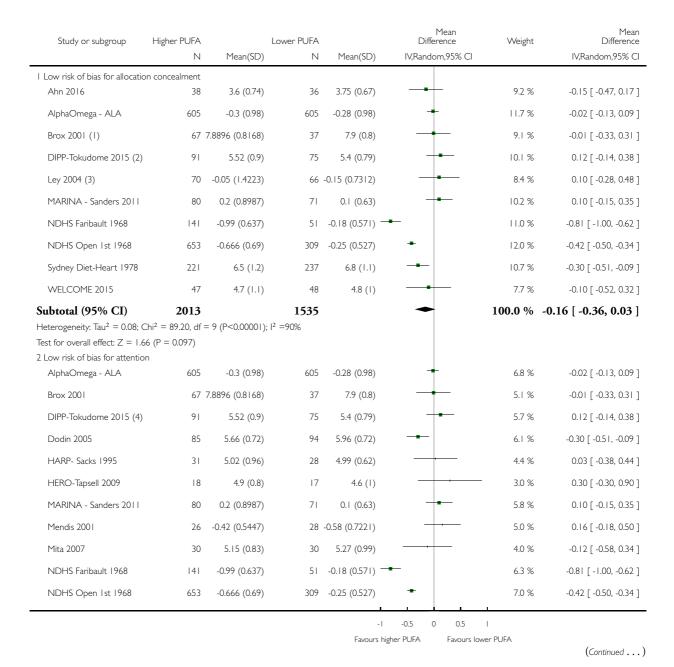


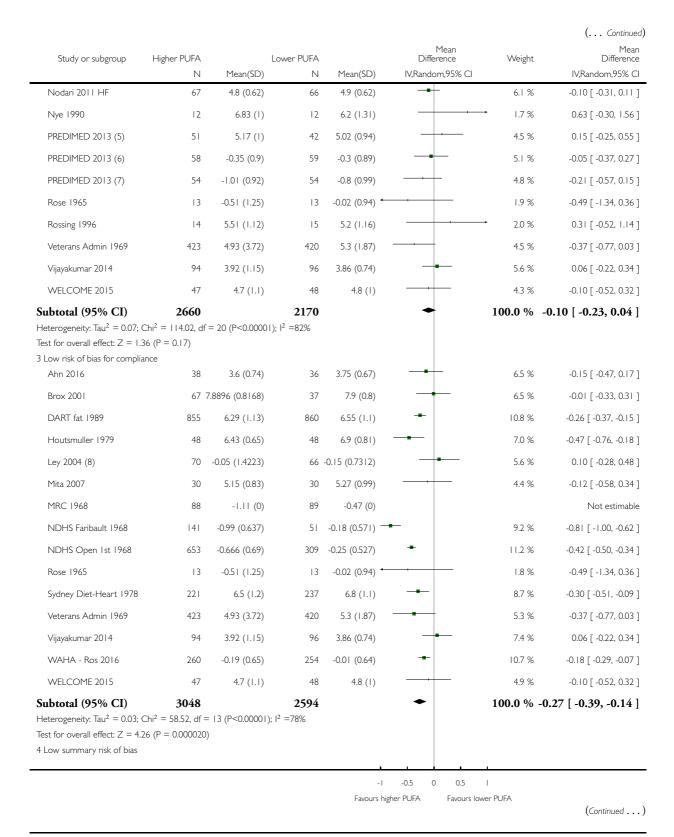
- (I) 14 month data, cod liver oil % seal oil combined
- (2) 2 year data
- (3) Change data
- (4) G2 arm data used
- (5) Arms A, B % E combined vs D (control), 52 week data, change data
- (6) Arms A, B % X combined vs D (control), 52 week data, change data
- (7) Damasceno 2013, Barcelona North subcohort, I year data
- (8) Barcelona hospital cohort at 5 years, Casas 2016
- (9) Fernandez-Real 2012, Reus subcohort, 2 year data

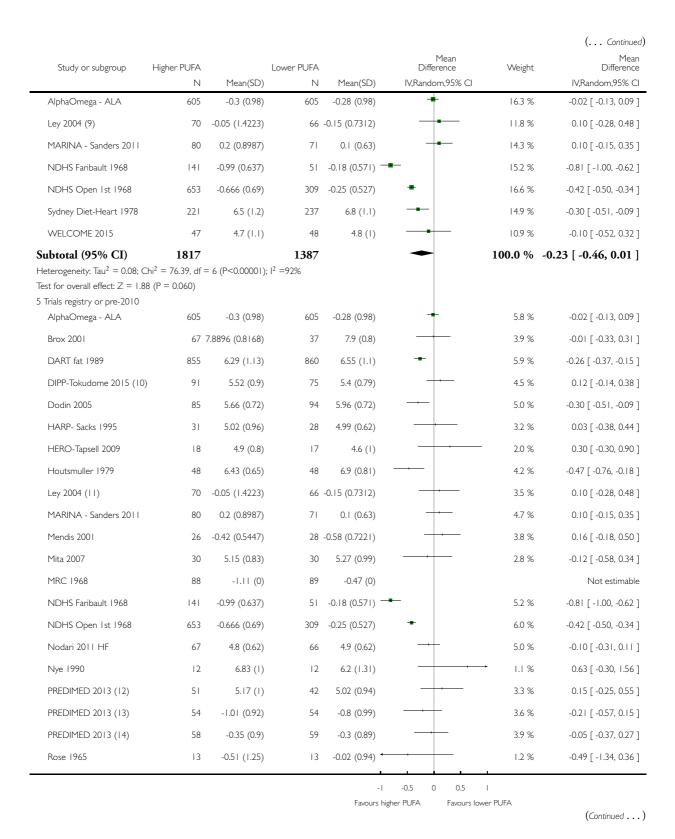
Analysis 3.29. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 29 TC, mmoL/L - SA.

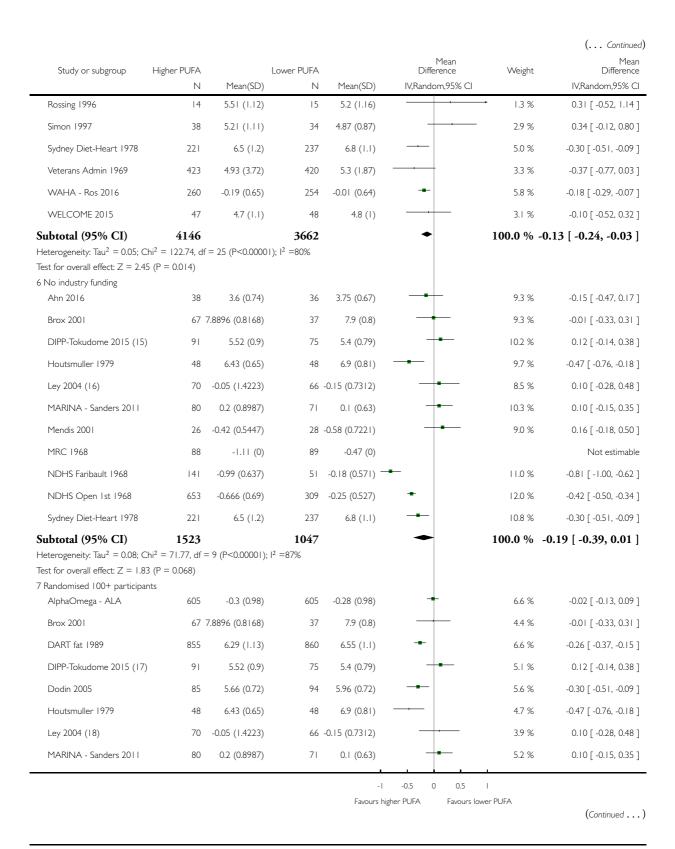
Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

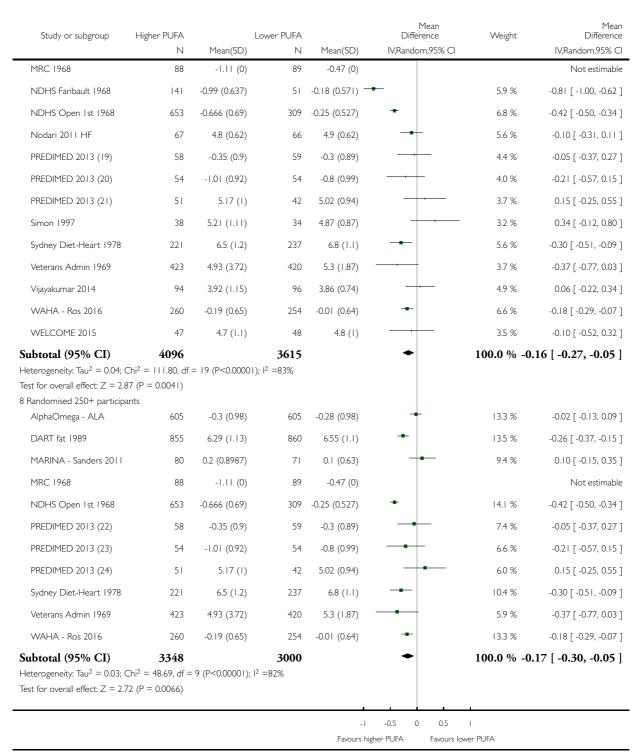
Outcome: 29 TC, mmoL/L - SA











- (I) I4 month data
- (2) 2-year data
- (3) Change data
- (4) 2-year data
- (5) Fernandez-Real 2012, Reus subcohort, 2 year data
- (6) Damasceno 2013, Barcelona North subcohort, I year data
- (7) Barcelona hospital cohort at 5 years, Casas 2016
- (8) Change data
- (9) Change data
- (10) 2-year data
- (11) Change data
- (12) Fernandez-Real 2012, Reus subcohort, 2 year data
- (13) Barcelona hospital cohort at 5 years, Casas 2016
- (14) Damasceno 2013, Barcelona North subcohort, I year data
- (15) 2-year data
- (16) Change data
- (17) 2-year data
- (18) Change data
- (19) Damasceno 2013, Barcelona North subcohort, I year data
- (20) Barcelona hospital cohort at 5 years, Casas 2016
- (21) Fernandez-Real 2012, Reus subcohort, 2 year data
- (22) Damasceno 2013, Barcelona North subcohort, I year data
- (23) Barcelona hospital cohort at 5 years, Casas 2016
- (24) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.30. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 30 TC, mmoL/L - SA fixed-effect.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 30 TC, mmoL/L - SA fixed-effect

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		1.5 %	-0.15 [-0.47, 0.17]
AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)		12.5 %	-0.02 [-0.13, 0.09]
Brox 2001	67	7.8896 (0.8168)	37	7.9 (0.8)		1.5 %	-0.01 [-0.33, 0.31]
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)		13.7 %	-0.26 [-0.37, -0.15]
DIPP-Tokudome 2015 (1)	91	5.52 (0.9)	75	5.4 (0.79)		2.3 %	0.12 [-0.14, 0.38]
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72)		3.4 %	-0.30 [-0.51, -0.09]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)		0.9 %	0.03 [-0.38, 0.44]
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)		0.4 %	0.30 [-0.30, 0.90]
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)	4	1.8 %	-0.47 [-0.76, -0.18]
Ley 2004 (2)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		1.1 %	0.10 [-0.28, 0.48]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		2.5 %	0.10 [-0.15, 0.35]
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		- 1.3 %	0.16 [-0.18, 0.50]
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99)		0.7 %	-0.12 [-0.58, 0.34]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable
NDHS Faribault 1968	141	-0.99 (0.637)	51	-0.18 (0.571)	•	4.3 %	-0.81 [-1.00, -0.62]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)	-	24.4 %	-0.42 [-0.50, -0.34]
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		3.4 %	-0.10 [-0.31, 0.11]
Nye 1990	12	6.83 (1)	12	6.2 (1.31)		0.2 %	0.63 [-0.30, 1.56]
PREDIMED 2013 (3)	54	-1.01 (0.92)	54	-0.8 (0.99)		1.2 %	-0.21 [-0.57, 0.15]
PREDIMED 2013 (4)	58	-0.35 (0.9)	59	-0.3 (0.89)		1.4 %	-0.05 [-0.37, 0.27]
PREDIMED 2013 (5)	51	5.17 (1)	42	5.02 (0.94)		1.0 %	0.15 [-0.25, 0.55]
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94)	-	0.2 %	-0.49 [-1.34, 0.36]
Rossing 1996	14	5.51 (1.12)	15	5.2 (1.16)	-	0.2 %	0.31 [-0.52, 1.14]
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)		0.7 %	0.34 [-0.12, 0.80]

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(Continued . . .)

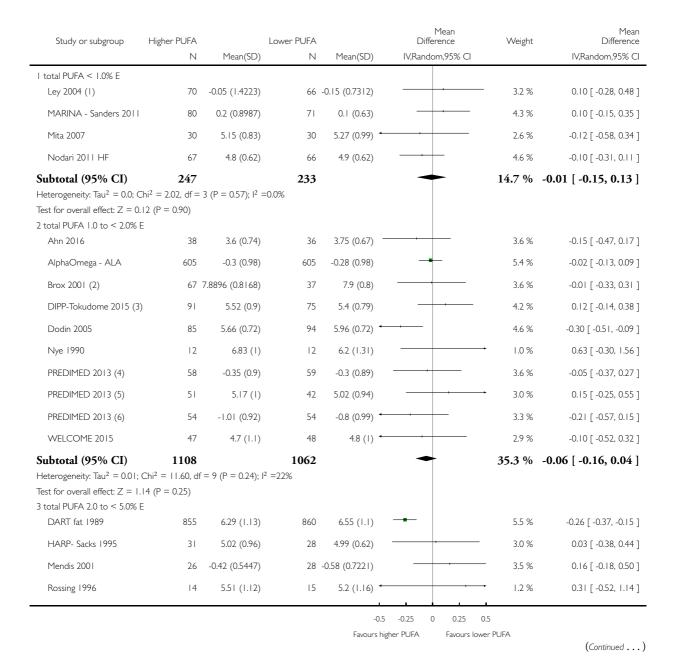
(... Continued) Mean Difference Mean Difference Higher PUFA Study or subgroup Lower PUFA Weight IV.Fixed.95% CI IV,Fixed,95% CI Ν Mean(SD) Ν Mean(SD) 221 -0.30 [-0.51, -0.09] Sydney Diet-Heart 1978 6.5 (1.2) 237 6.8 (1.1) 3.4 % Veterans Admin 1969 5.3 (1.87) -0.37 [-0.77, 0.03] 423 4.93 (3.72) 420 1.0 % Vijayakumar 2014 94 3.92 (1.15) 96 3.86 (0.74) 2.0 % 0.06 [-0.22, 0.34] WAHA - Ros 2016 -0.18 [-0.29, -0.07] 260 -0.19 (0.65) -0.01 (0.64) 12.2 % 254 WELCOME 2015 -0.10 [-0.52, 0.32] 47 4.7 (1.1) 4.8 (I) 0.9 % 48 **Total (95% CI)** 4278 3794 100.0 % -0.22 [-0.26, -0.18] Heterogeneity: $Chi^2 = 127.12$, df = 27 (P<0.00001); $I^2 = 79\%$ Test for overall effect: Z = 11.21 (P < 0.00001)Test for subgroup differences: Not applicable 0.25 0.5 -0.5 -0.25 0 Favours higher PUFA Favours lower PUFA

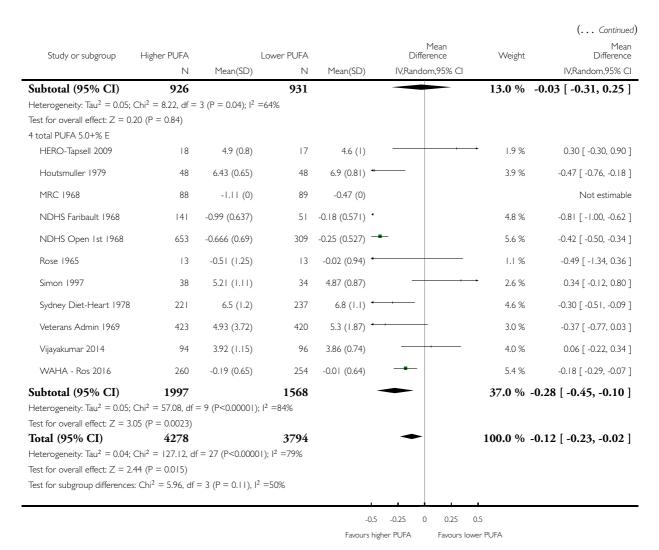
- (I) 2 year data
- (2) Change data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.31. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 31 TC, mmoL/L - subgroup by PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 31 TC, mmoL/L - subgroup by PUFA dose



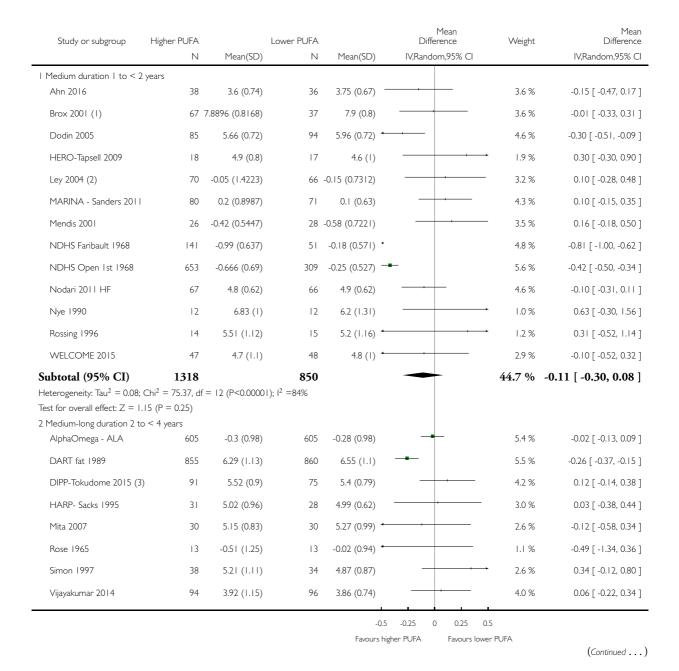


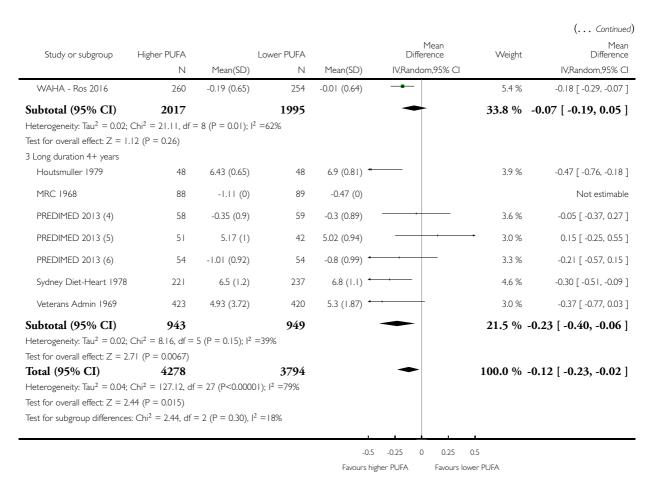
- (I) Change data
- (2) 14 month data
- (3) 2-year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Fernandez-Real 2012, Reus subcohort, 2 year data
- (6) Barcelona hospital cohort at 5 years, Casas 2016

Analysis 3.32. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 32 TC, mmoL/L - subgroup by duration.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 32 TC, mmoL/L - subgroup by duration



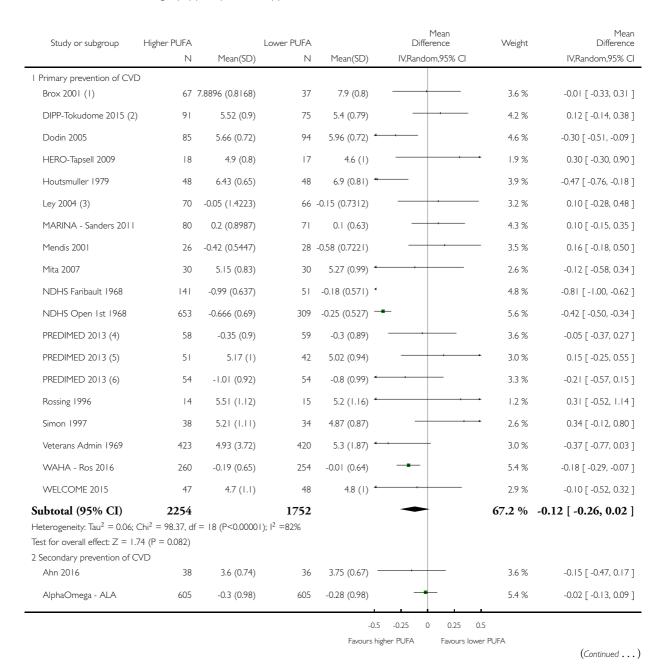


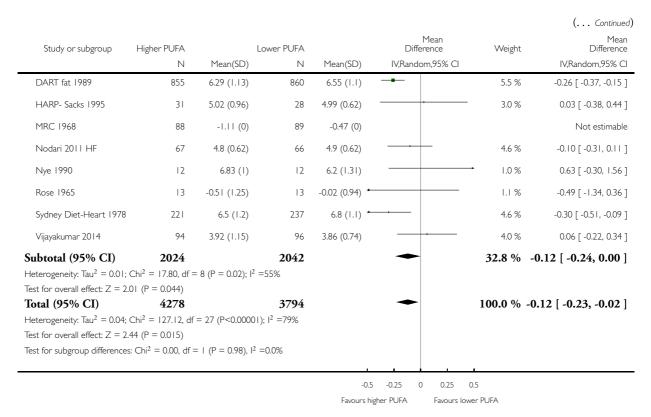
- (I) I4 month data
- (2) Change data
- (3) 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Fernandez-Real 2012, Reus subcohort, 2 year data
- (6) Barcelona hospital cohort at 5 years, Casas 2016

Analysis 3.33. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 33 TC, mmoL/L - subgroup by primary or secondary prevention.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 33 TC, mmoL/L - subgroup by primary or secondary prevention



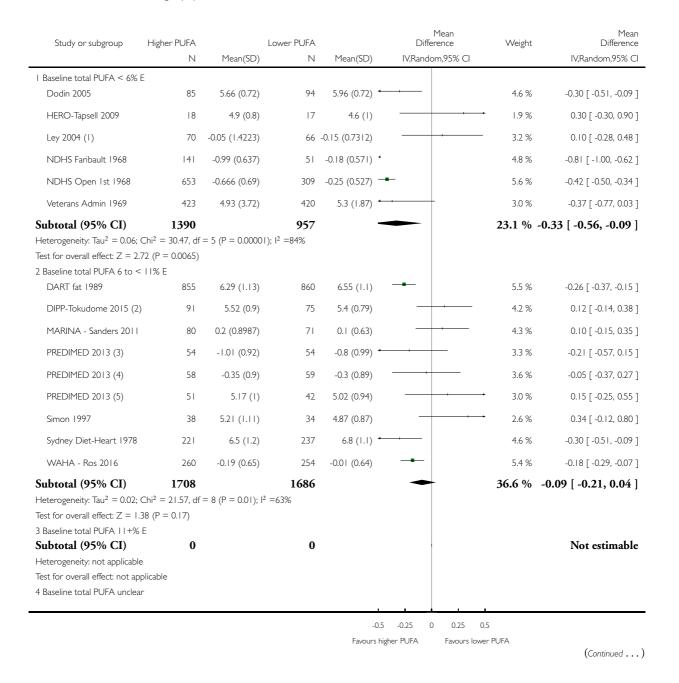


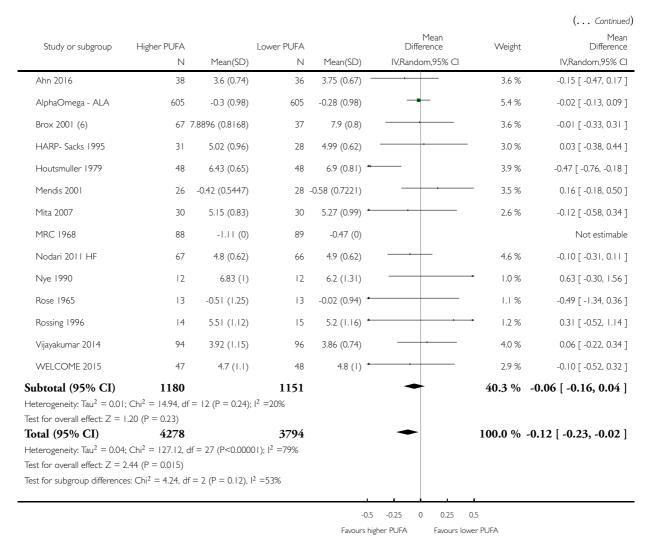
- (I) I4 month data
- (2) 2 year data
- (3) Change data
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Fernandez-Real 2012, Reus subcohort, 2 year data
- (6) Barcelona hospital cohort at 5 years, Casas 2016

Analysis 3.34. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 34 TC, mmoL/L - subgroup by baseline PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 34 TC, mmoL/L - subgroup by baseline PUFA dose



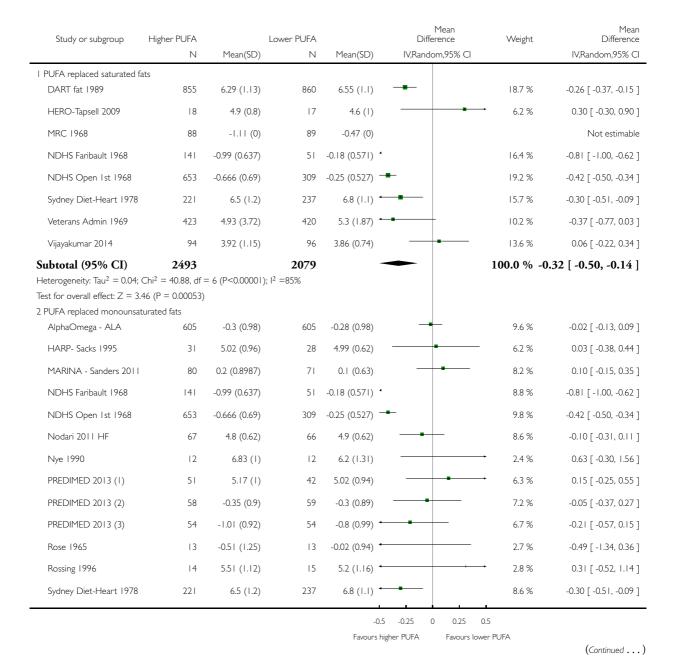


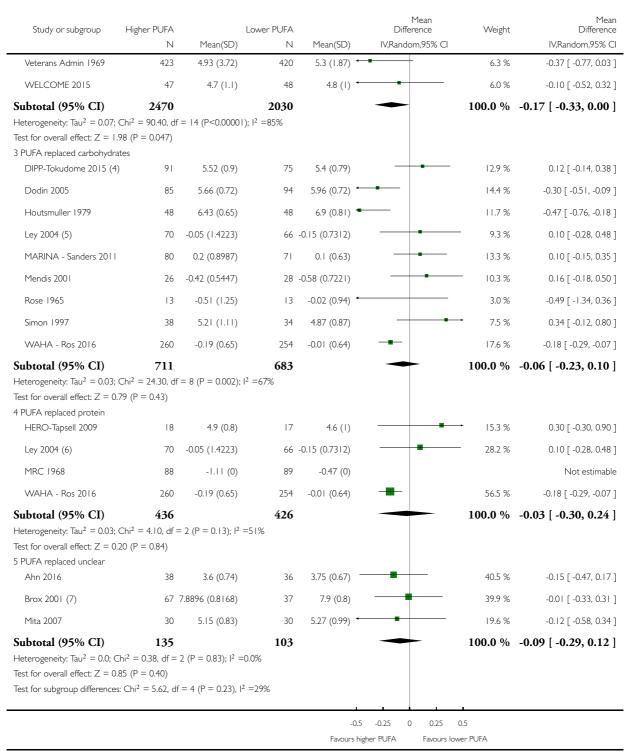
- (I) Change data
- (2) 2 year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Fernandez-Real 2012, Reus subcohort, 2 year data
- (6) 14 month data

Analysis 3.35. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 35 TC, mmoL/L - subgroup by replacement.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 35 TC, mmoL/L - subgroup by replacement





- (I) Fernandez-Real 2012, Reus subcohort, 2 year data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) 2 year data
- (5) Change data
- (6) Change data
- (7) 14 month data

Analysis 3.36. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 36 TC, mmoL/L - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

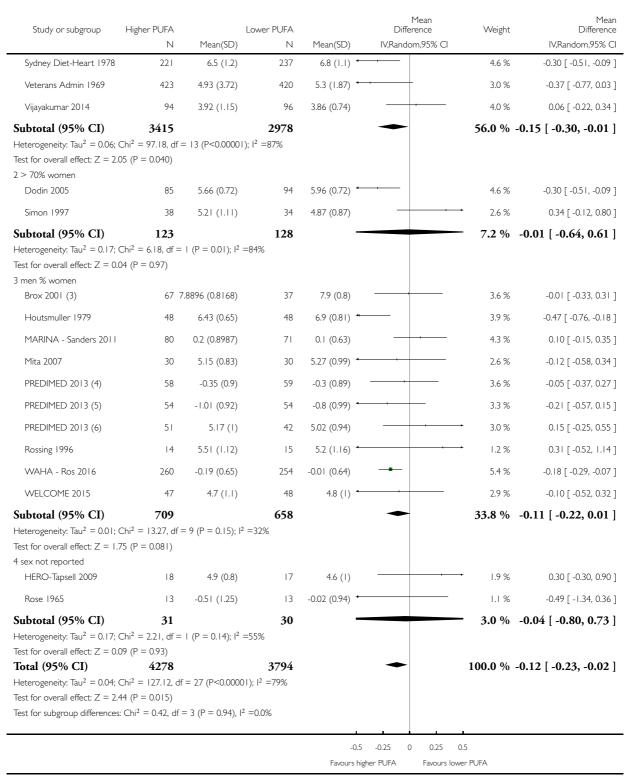
Outcome: 36 TC, mmoL/L - subgroup by sex

Study or subgroup	Higher PUFA	Lower PUFA			Mean Difference	Weight	Mean Difference	
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,959	ś CI	IV,Random,95% CI	
I > 70% men								
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		3.6 %	-0.15 [-0.47, 0.17]	
AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)	-	5.4 %	-0.02 [-0.13, 0.09]	
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)		5.5 %	-0.26 [-0.37, -0.15]	
DIPP-Tokudome 2015 (1)	91	5.52 (0.9)	75	5.4 (0.79)		4.2 %	0.12 [-0.14, 0.38]	
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)		3.0 %	0.03 [-0.38, 0.44]	
Ley 2004 (2)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		3.2 %	0.10 [-0.28, 0.48]	
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		3.5 %	0.16 [-0.18, 0.50]	
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable	
NDHS Faribault 1968	141	-0.99 (0.637)	51	-0.18 (0.571)	•	4.8 %	-0.81 [-1.00, -0.62]	
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)	-	5.6 %	-0.42 [-0.50, -0.34]	
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		4.6 %	-0.10 [-0.31, 0.11]	
Nye 1990	12	6.83 (I)	12	6.2 (1.31)		1.0 %	0.63 [-0.30, 1.56]	
				-().5 -0.25 O C	.25 0.5		

Favours higher PUFA

Favours lower PUFA

(Continued . . .)



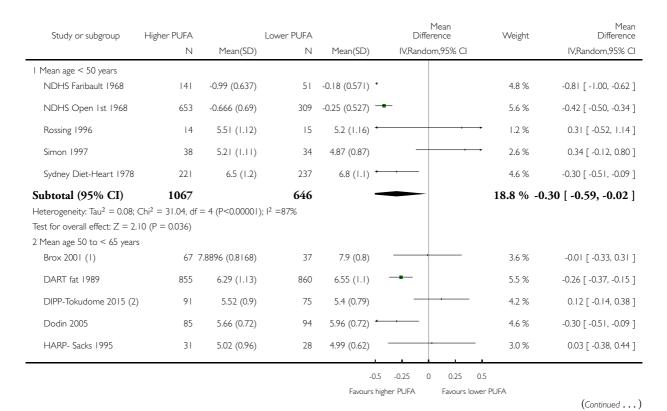
- (I) 2 year data
- (2) Change data
- (3) 14 month data
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Barcelona hospital cohort at 5 years, Casas 2016
- (6) Fernandez-Real 2012, Reus subcohort, 2 year data

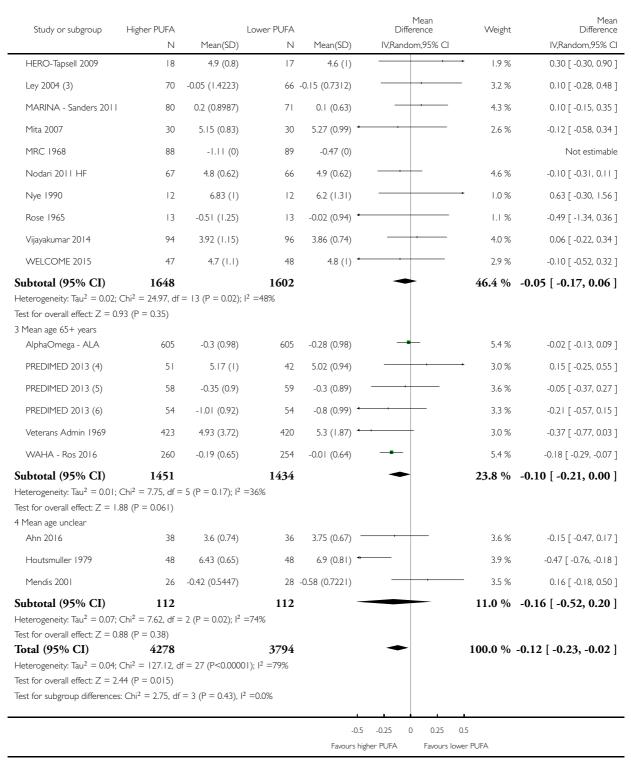
Analysis 3.37. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 37 TC, mmoL/L - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 37 TC, mmoL/L - subgroup by age





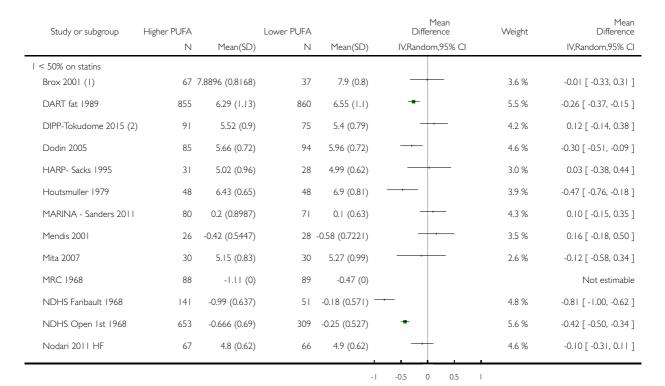
- (I) I4 month data
- (2) 2 year data
- (3) Change data
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Barcelona hospital cohort at 5 years, Casas 2016

Analysis 3.38. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 38 TC, mmoL/L - subgroup by statin use.

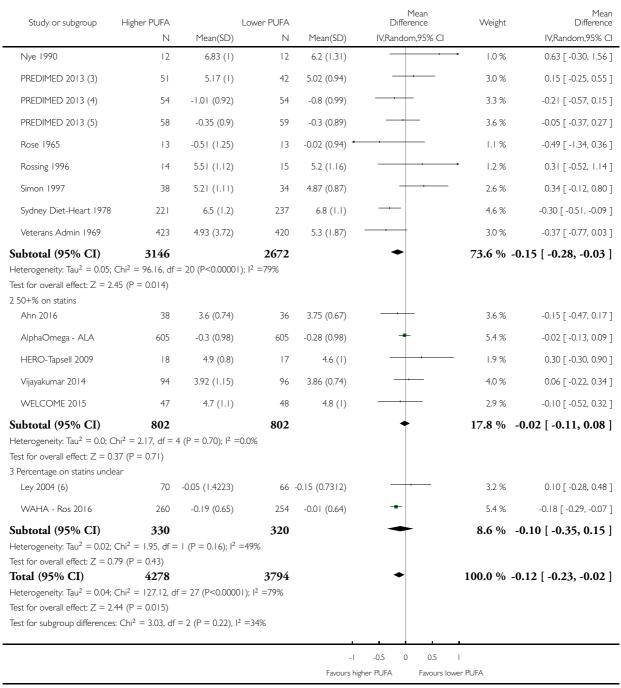
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 38 TC, mmoL/L - subgroup by statin use



Favours higher PUFA Favours lower PUFA (Continued . . .)



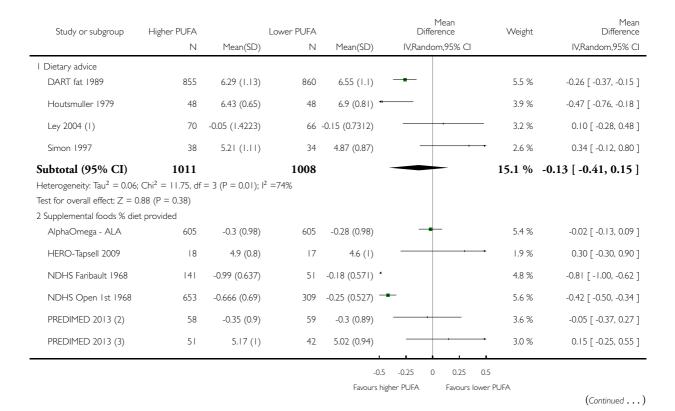
- (I) I4 month data
- (2) 2 year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casas 2016
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Change data

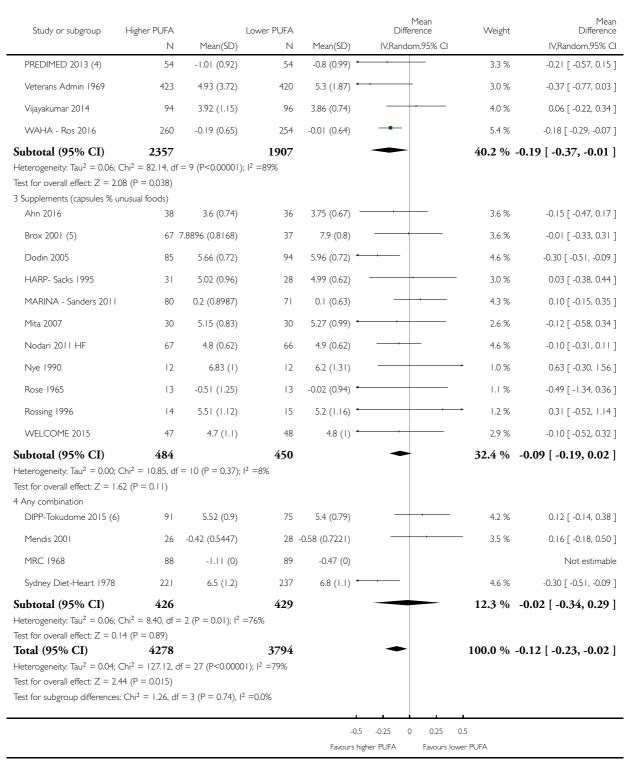
Analysis 3.39. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 39 TC, mmoL/L - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 39 TC, mmoL/L - subgroup by intervention type





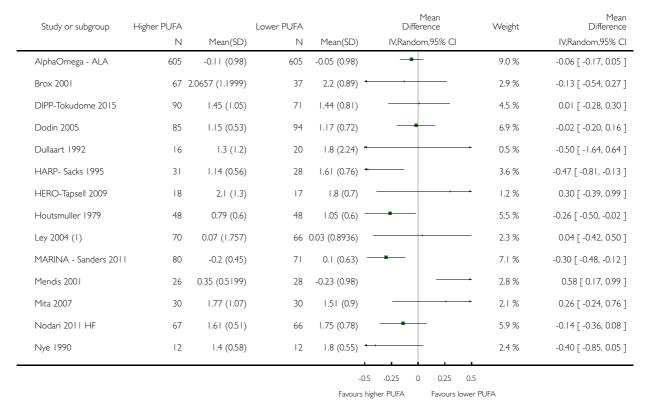
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casas 2016
- (5) 14 month data
- (6) 2 year data

Analysis 3.40. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 40 Serum fasting TRIGLYCERIDE (TG, mmoL/L).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 40 Serum fasting TRIGLYCERIDE (TG, mmoL/L)



(Continued ...)

(... Continued) Mean Difference Mean Difference Study or subgroup Higher PUFA Lower PUFA Weight Ν Mean(SD) Ν Mean(SD) IV.Random.95% CI IV,Random,95% CI -0.38 [-0.57, -0.19] ORL 2013 170 -0.78 (0.9) 165 -0.4 (0.87) 6.7 % PREDIMED 2013 (2) -0.14 [-0.35, 0.07] 58 -0.18 (0.58) 59 -0.04 (0.58) 6.2 % PREDIMED 2013 (3) 54 -0.28 (0.77) -0.25 (0.84) 4.2 % -0.03 [-0.33, 0.27] PREDIMED 2013 (4) 51 1.27 (0.58) 42 4.9 % -0.13 [-0.39, 0.13] 1.4 (0.7) Simon 1997 -0.10 [-0.50, 0.30] 37 1.25 (0.61) 34 1.35 (1.05) 2.9 % Sydney Diet-Heart 1978 -0.10 [-0.26, 0.06] 221 1.6 (0.9) 237 1.7 (0.9) 7.4 % Vijayakumar 2014 94 1.27 (0.51) 96 1.23 (0.53) 7.9 % 0.04 [-0.11, 0.19] WELCOME 2015 47 1.5 (1.2) 48 1.8 (0.6) 3.1 % -0.30 [-0.68, 0.08] **Total (95% CI)** 1977 1928 100.0 % -0.12 [-0.20, -0.04] Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 42.24$, df = 21 (P = 0.004); $I^2 = 50\%$ Test for overall effect: Z = 2.84 (P = 0.0046) Test for subgroup differences: Not applicable -0.5 -0.25 0.25 0.5

Favours higher PUFA

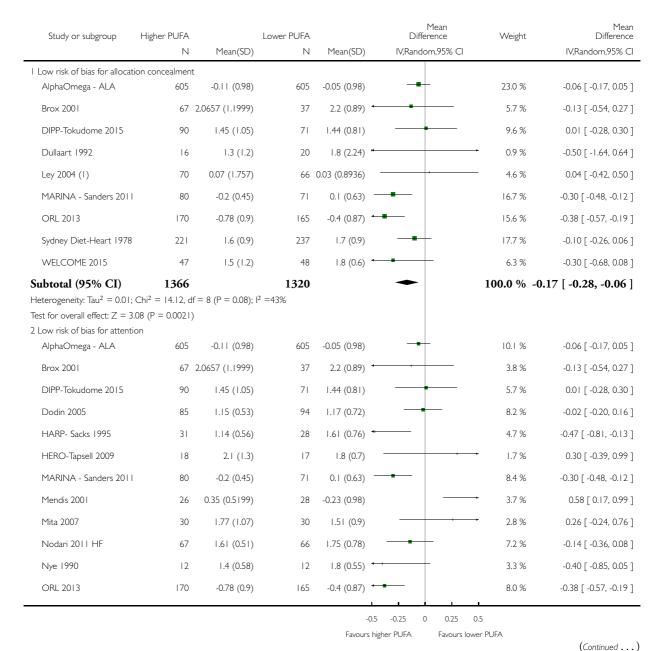
Favours lower PUFA

- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data

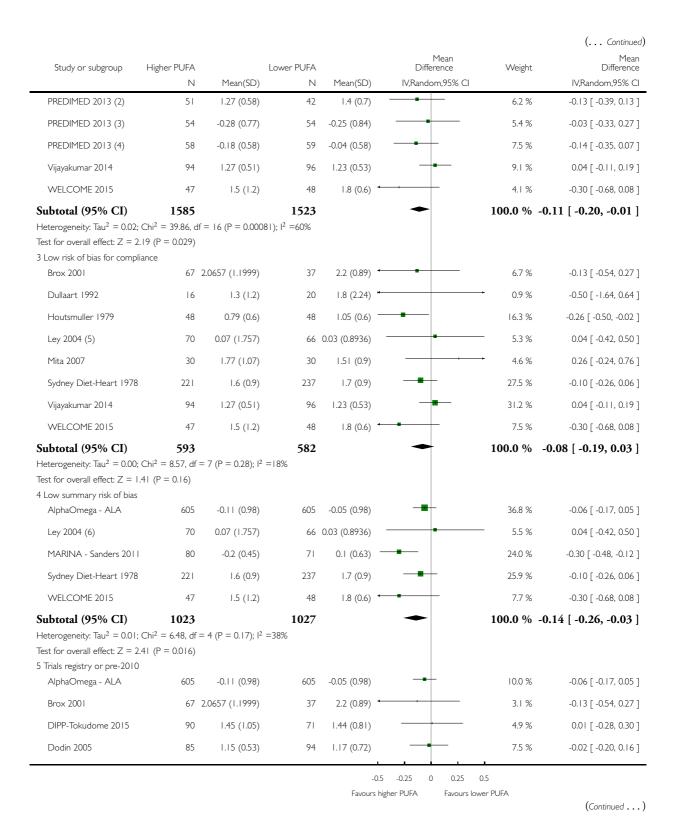
Analysis 3.41. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 41 TG, mmoL/L - SA.

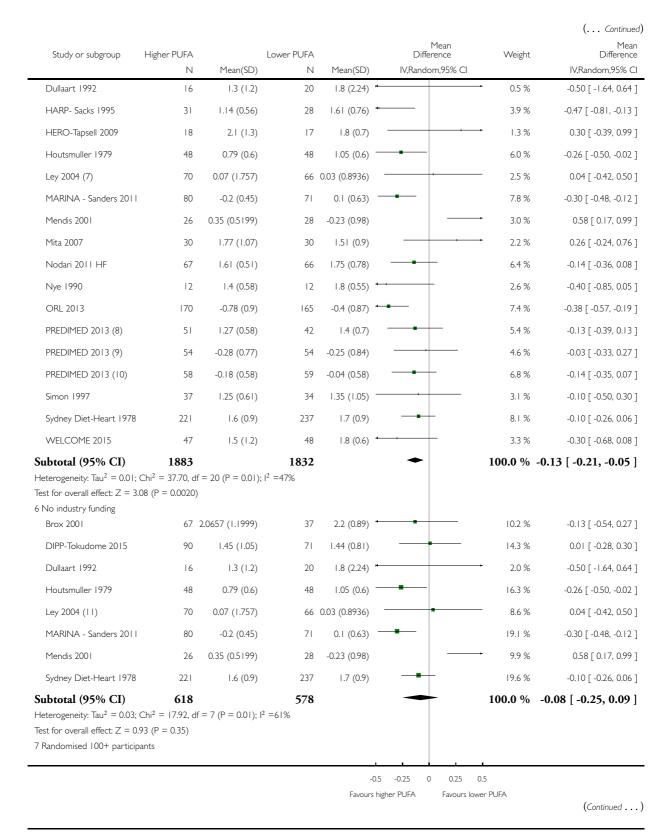
Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

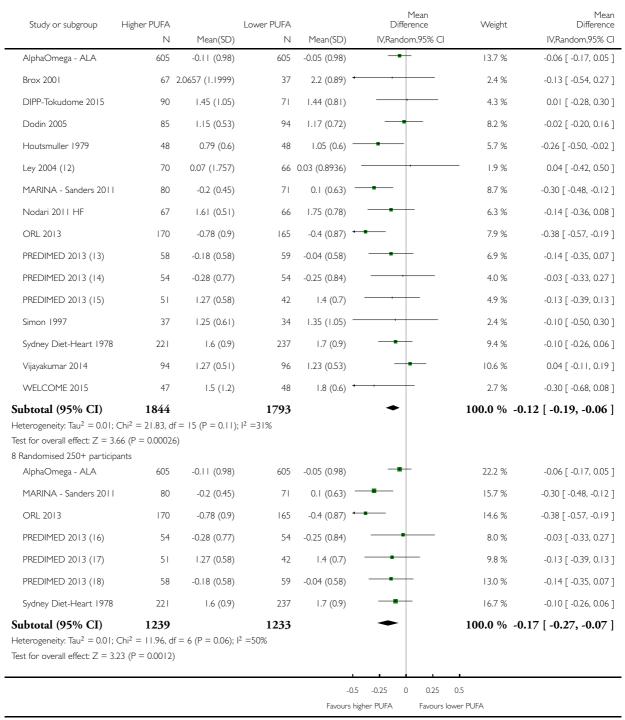
Outcome: 41 TG, mmoL/L - SA



(continued ...







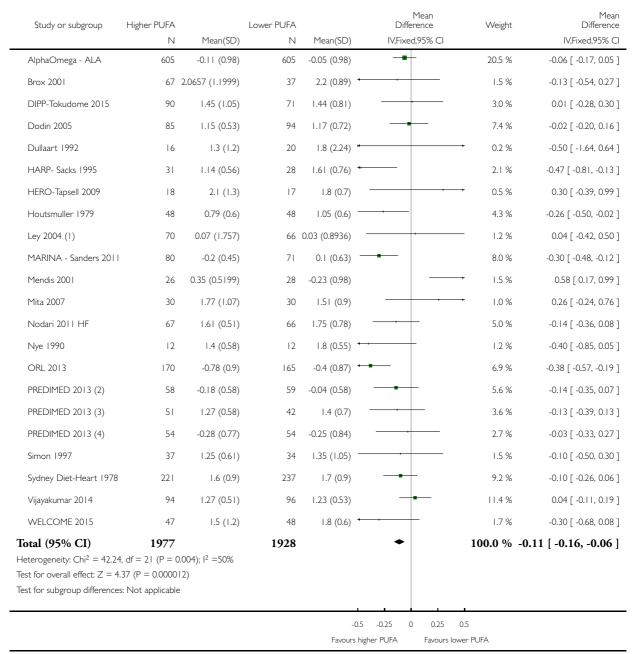
- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Change data
- (6) Change data
- (7) Change data
- (8) Fernandez-Real 2012, Reus subcohort, 2 year data
- (9) Barcelona hospital cohort at 5 years, Casas 2016
- (10) Damasceno 2013, Barcelona North subcohort, I year data
- (11) Change data
- (12) Change data
- (13) Damasceno 2013, Barcelona North subcohort, I year data
- (14) Barcelona hospital cohort at 5 years, Casas 2016
- (15) Fernandez-Real 2012, Reus subcohort, 2 year data
- (16) Barcelona hospital cohort at 5 years, Casas 2016
- (17) Fernandez-Real 2012, Reus subcohort, 2 year data
- (18) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.42. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 42 TG, mmoL/L - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 42 TG, mmoL/L - SA fixed-effect

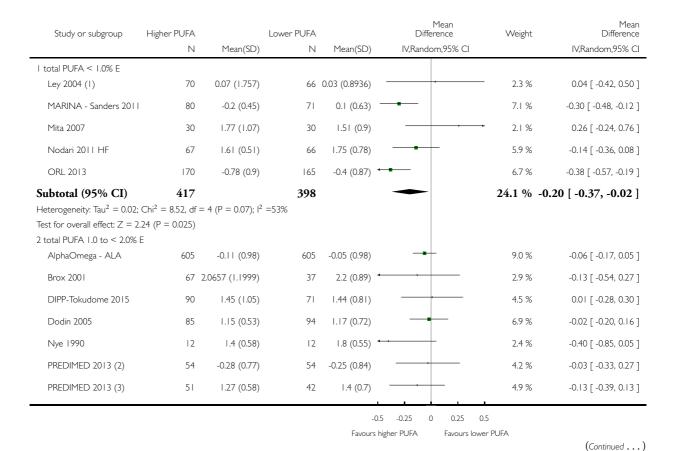


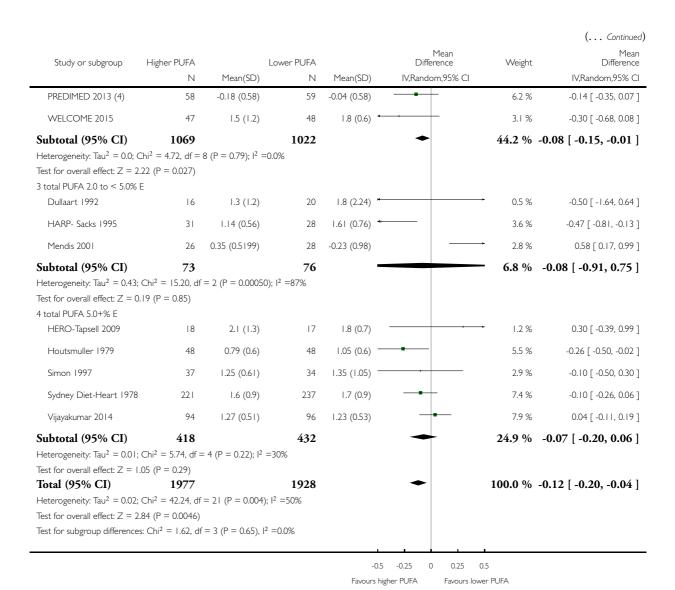
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casas 2016

Analysis 3.43. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 43 TG, mmoL/L - subgroup by PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 43 TG, mmoL/L - subgroup by PUFA dose



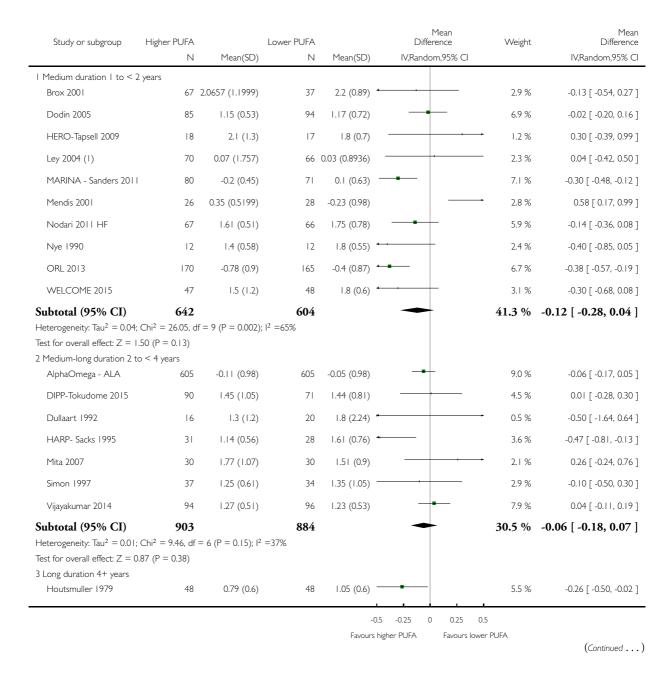


- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casas 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.44. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 44 TG, mmoL/L - subgroup by duration.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 44 TG, mmoL/L - subgroup by duration



(... Continued) Mean Difference Mean Difference Study or subgroup Higher PUFA Lower PUFA Weight Ν Mean(SD) Ν Mean(SD) IV.Random.95% CI IV,Random,95% CI -0.14 [-0.35, 0.07] PREDIMED 2013 (2) 58 -0.18 (0.58) 59 -0.04 (0.58) 6.2 % PREDIMED 2013 (3) -0.03 [-0.33, 0.27] 54 -0.28 (0.77) 54 -0.25 (0.84) 4.2 % PREDIMED 2013 (4) 51 1.27 (0.58) 42 1.4 (0.7) 4.9 % -0.13 [-0.39, 0.13] Sydney Diet-Heart 1978 221 1.6 (0.9) 237 1.7 (0.9) 7.4 % -0.10 [-0.26, 0.06] Subtotal (95% CI) 432 440 28.3 % -0.13 [-0.23, -0.03] Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.67$, df = 4 (P = 0.80); $I^2 = 0.0\%$ Test for overall effect: Z = 2.63 (P = 0.0086) **Total (95% CI)** 1977 1928 100.0 % -0.12 [-0.20, -0.04] Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 42.24$, df = 21 (P = 0.004); $I^2 = 50\%$ Test for overall effect: Z = 2.84 (P = 0.0046) Test for subgroup differences: $Chi^2 = 0.96$, df = 2 (P = 0.62), $I^2 = 0.0\%$ -0.5 -0.25 0.25

Favours higher PUFA

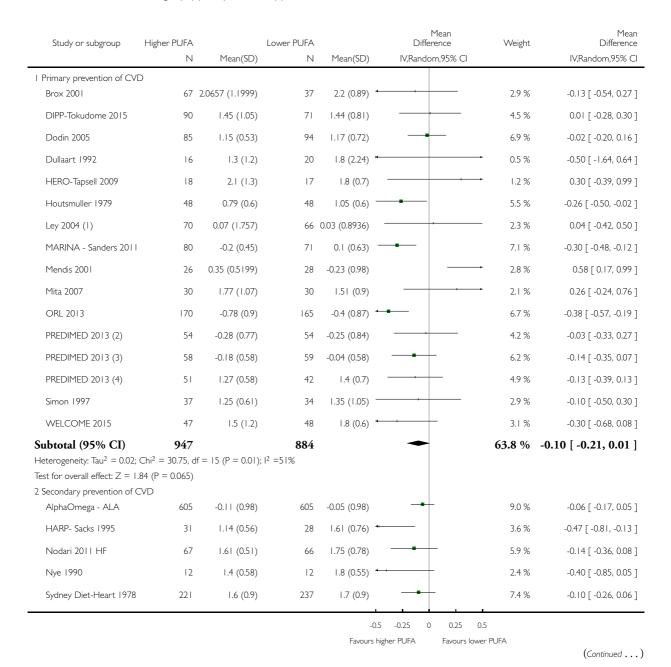
Favours lower PUFA

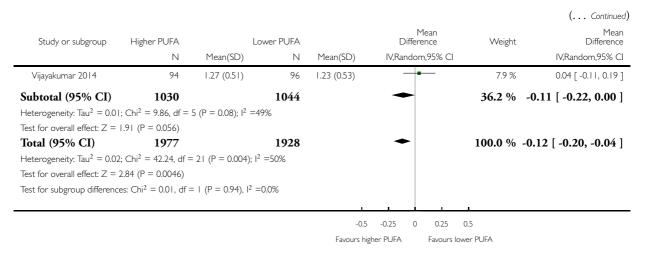
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.45. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 45 TG, mmoL/L - subgroup by primary or secondary prevention.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 45 TG, mmoL/L - subgroup by primary or secondary prevention



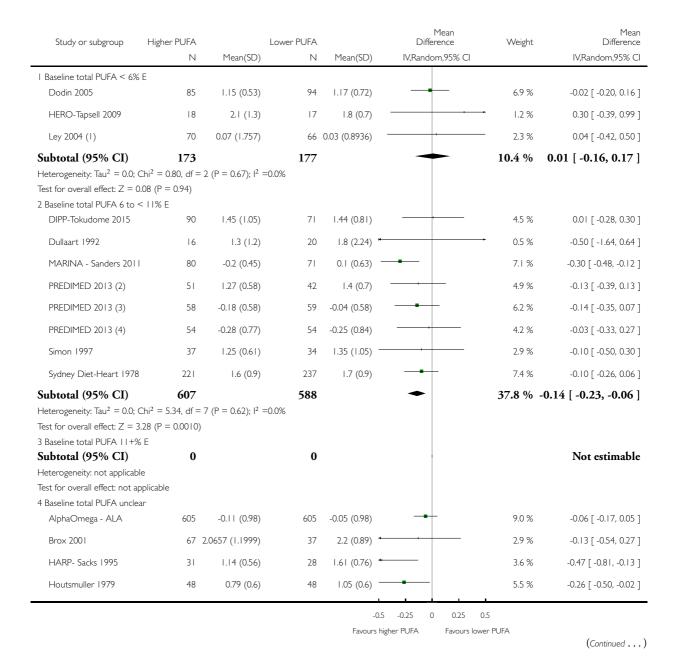


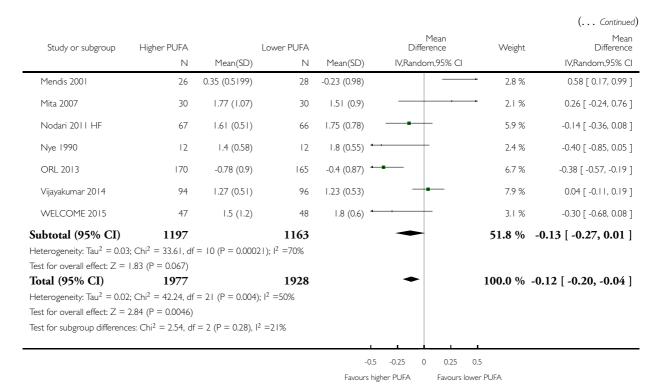
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casas 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.46. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 46 TG, mmoL/L - subgroup by baseline PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 46 TG, mmoL/L - subgroup by baseline PUFA dose



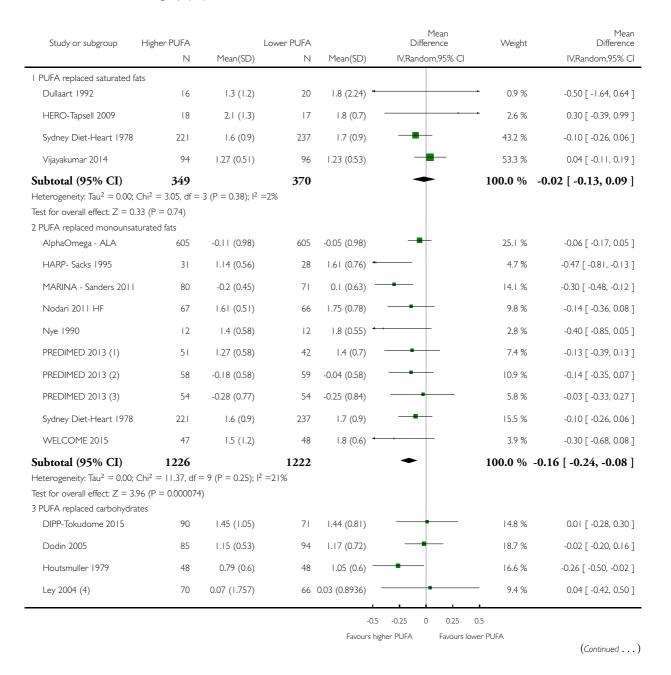


- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Barcelona hospital cohort at 5 years, Casas 2016

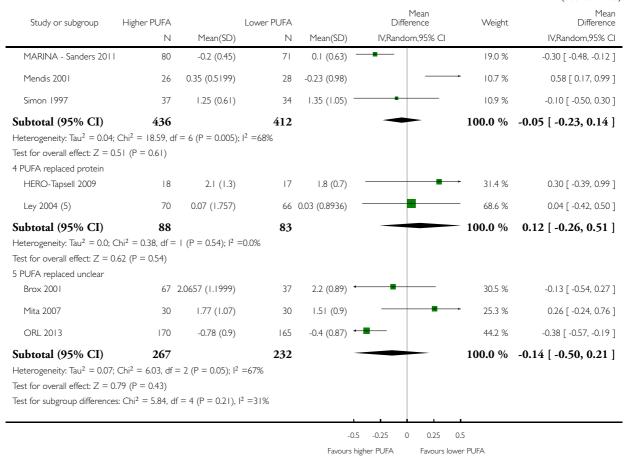
Analysis 3.47. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 47 TG, mmoL/L - subgroup by replacement.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 47 TG, mmoL/L - subgroup by replacement





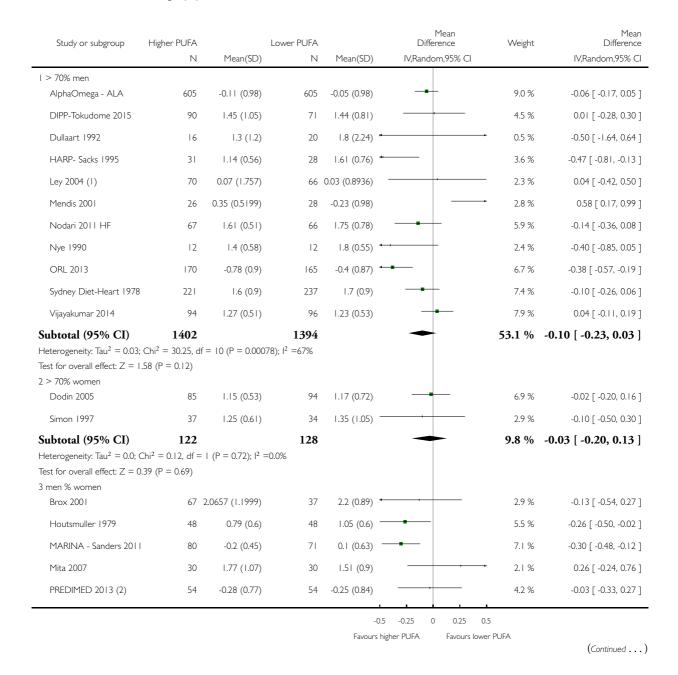


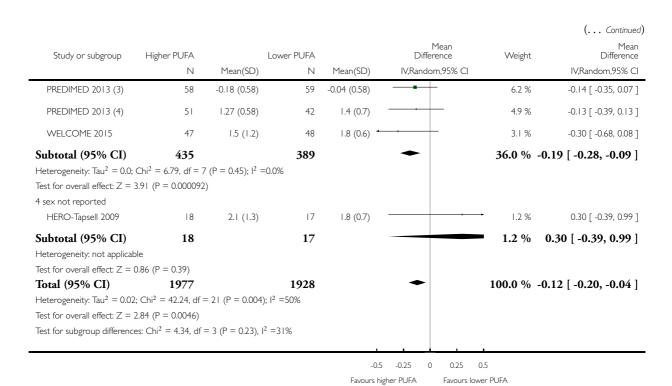
- (1) Fernandez-Real 2012, Reus subcohort, 2 year data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Change data
- (5) Change data

Analysis 3.48. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 48 TG, mmoL/L - subgroup by sex.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 48 TG, mmoL/L - subgroup by sex



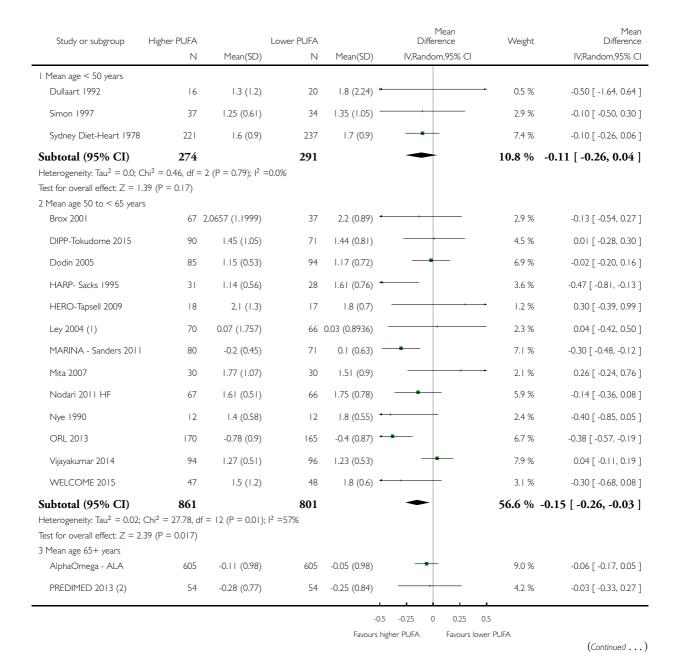


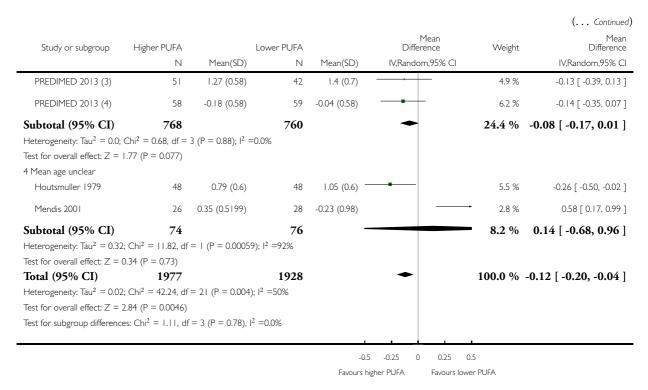
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casas 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.49. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 49 TG, mmoL/L - subgroup by age.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 49 TG, mmoL/L - subgroup by age



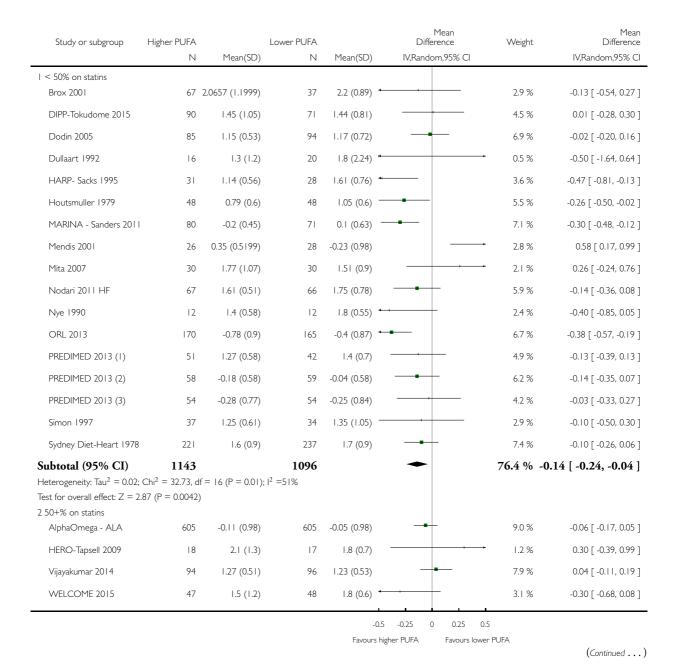


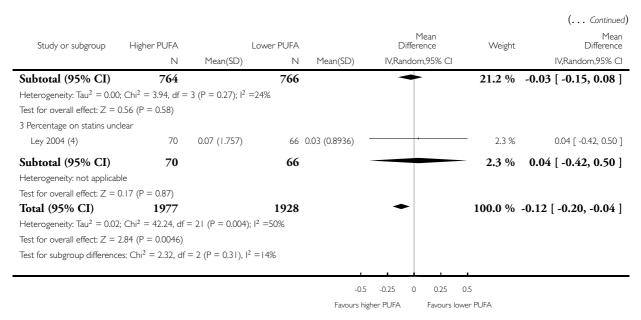
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casas 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.50. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 50 TG, mmoL/L - subgroup by statin use.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 50 TG, mmoL/L - subgroup by statin use



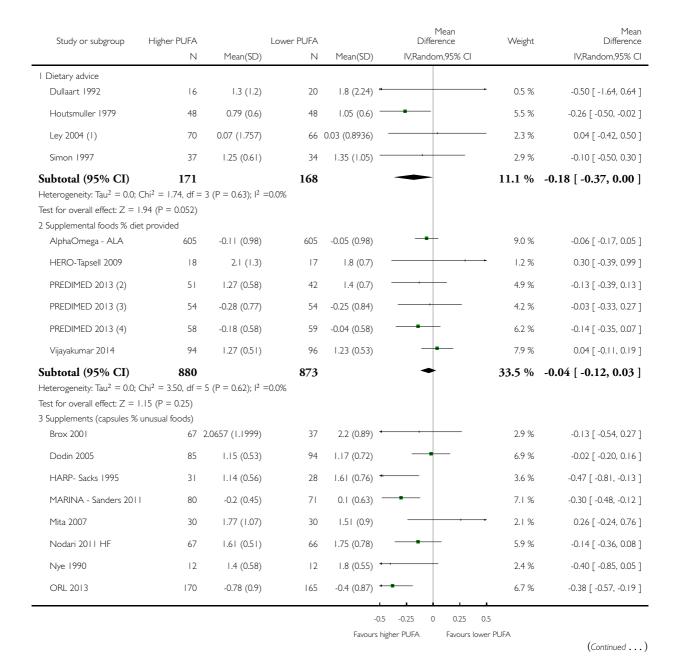


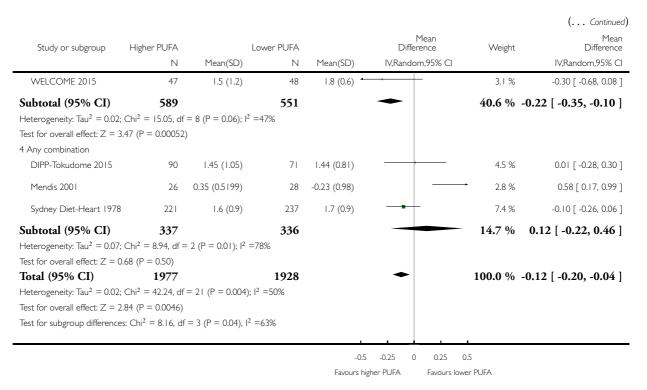
- (1) Fernandez-Real 2012, Reus subcohort, 2 year data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Change data

Analysis 3.51. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 51 TG, mmoL/L - subgroup by intervention type.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 51 TG, mmoL/L - subgroup by intervention type





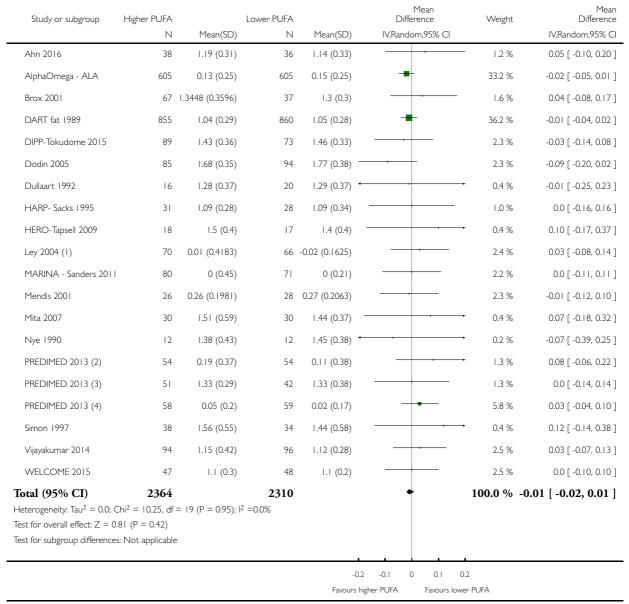
- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.52. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 52 Serum HIGH DENSITY LIPOPROTEIN (HDL, mmoL/L).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 52 Serum HIGH DENSITY LIPOPROTEIN (HDL, mmoL/L)



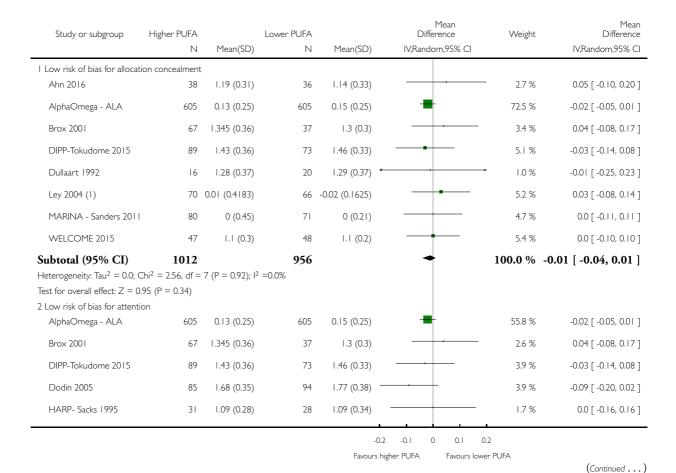
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

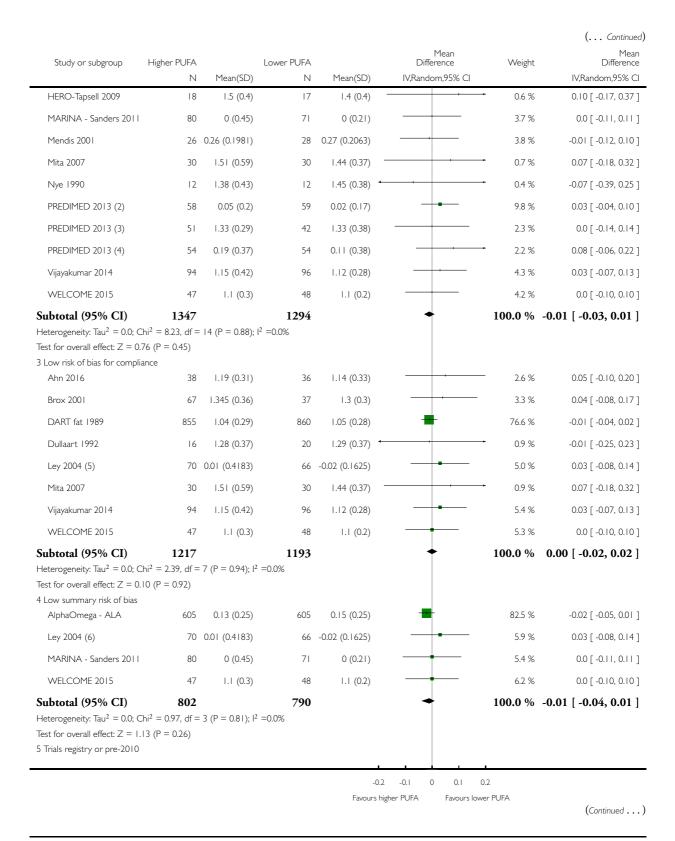
Analysis 3.53. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 53 HDL, mmoL/L - SA.

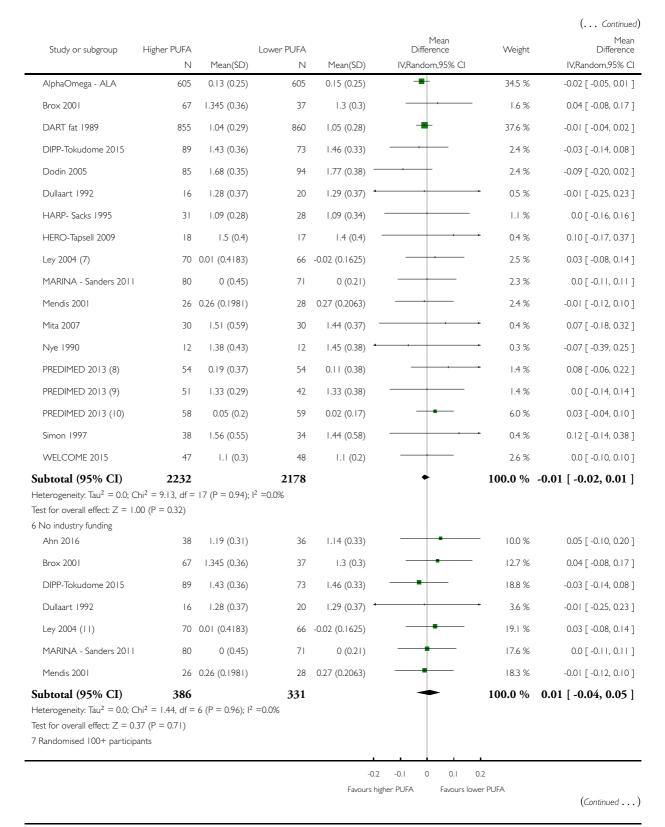
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

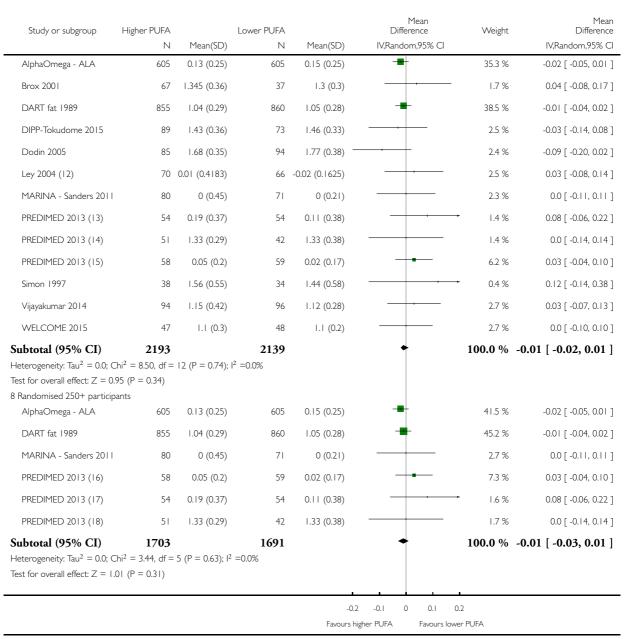
Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 53 HDL, mmoL/L - SA









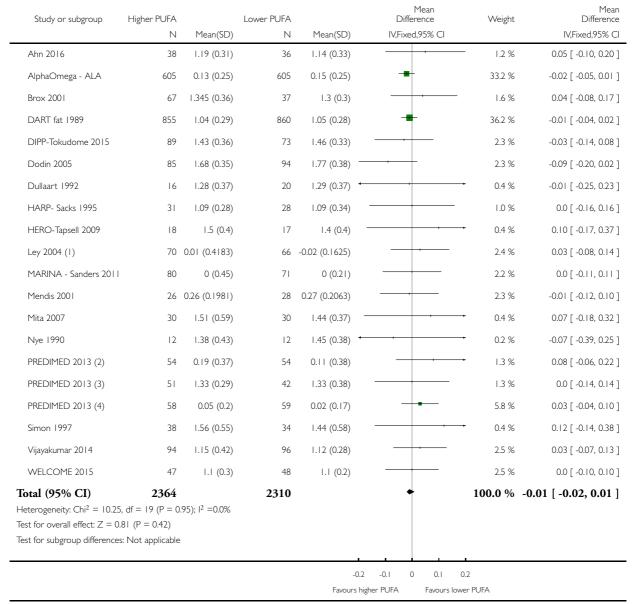
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Change data
- (6) Change data
- (7) Change data
- (8) Barcelona hospital cohort at 5 years, Casa 2016
- (9) Fernandez-Real 2012, Reus subcohort, 2 year data
- (10) Damasceno 2013, Barcelona North subcohort, I year data
- (11) Change data
- (12) Change data
- (13) Barcelona hospital cohort at 5 years, Casa 2016
- (14) Fernandez-Real 2012, Reus subcohort, 2 year data
- (15) Damasceno 2013, Barcelona North subcohort, I year data
- (16) Damasceno 2013, Barcelona North subcohort, I year data
- (17) Barcelona hospital cohort at 5 years, Casa 2016
- (18) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.54. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 54 HDL, mmoL/L - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 54 HDL, mmoL/L - SA fixed-effect

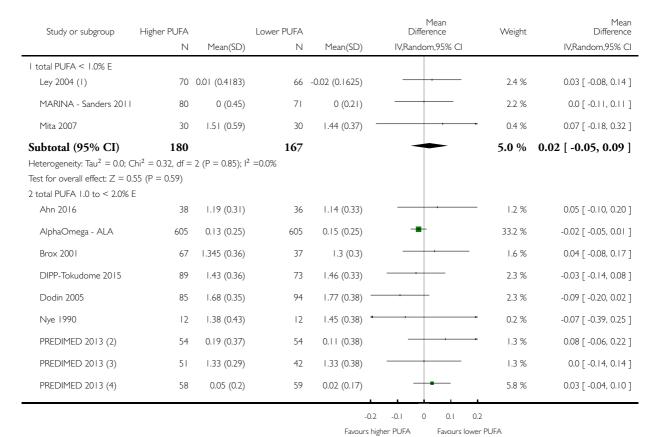


- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

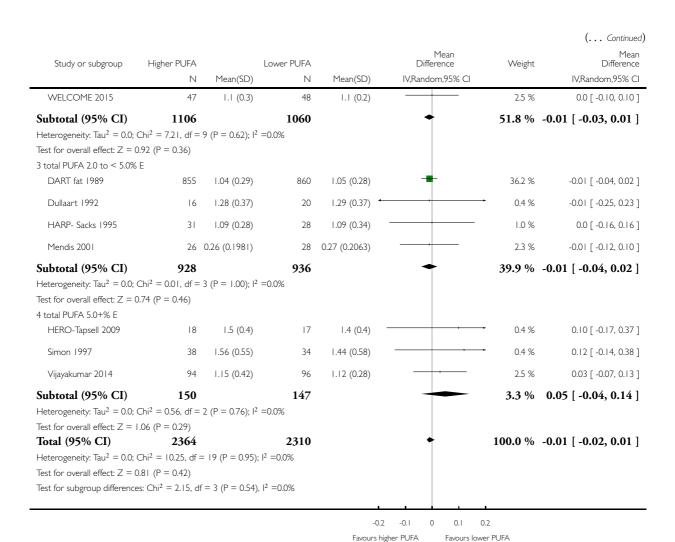
Analysis 3.55. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 55 HDL, mmoL/L - subgroup by PUFA dose.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 55 HDL, mmoL/L - subgroup by PUFA dose



(Continued . . .)



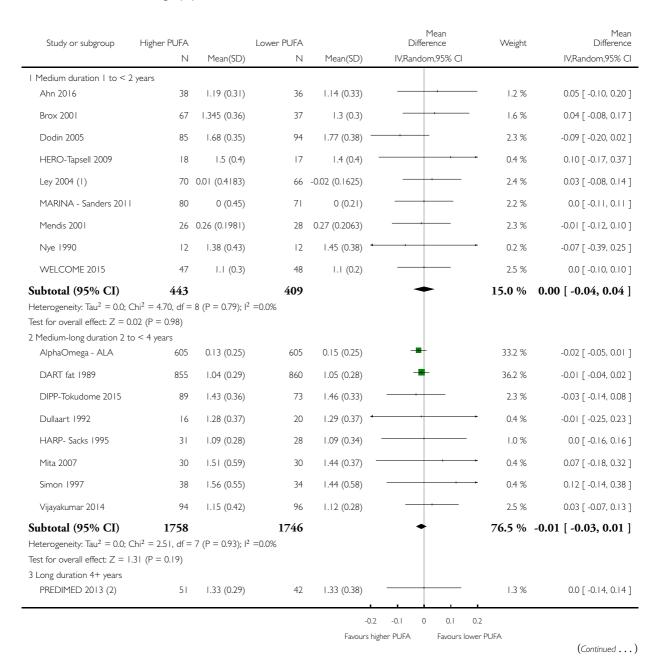
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

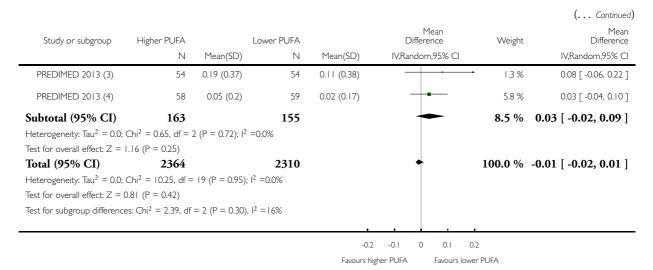
Analysis 3.56. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 56 HDL, mmoL/L - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 56 HDL, mmoL/L - subgroup by duration

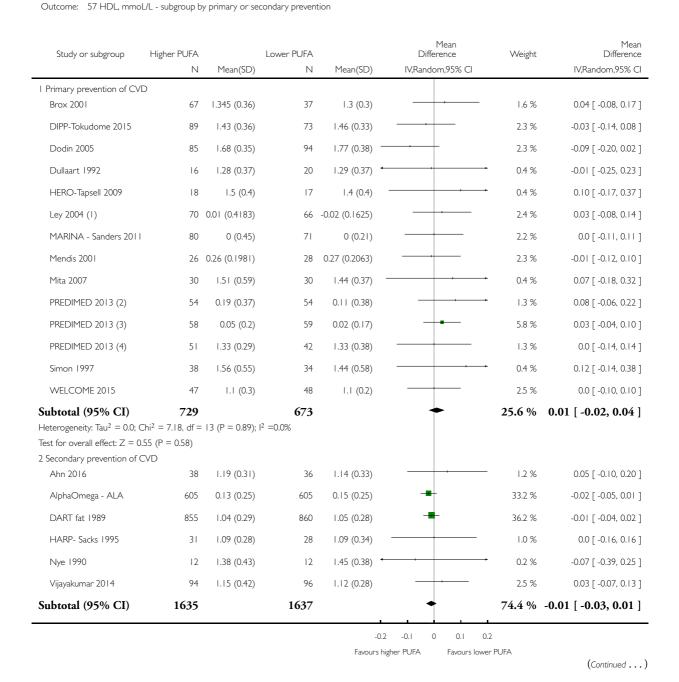


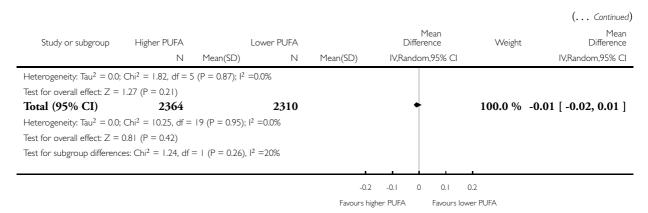


- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.57. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 57 HDL, mmoL/L - subgroup by primary or secondary prevention.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes





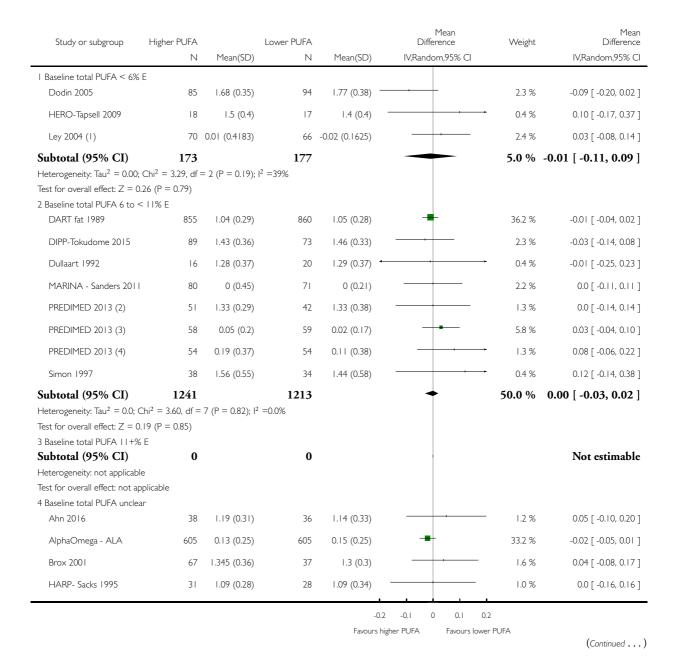
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.58. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 58 HDL, mmoL/L - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 58 HDL, mmoL/L - subgroup by baseline PUFA dose



(... Continued) Mean Difference Mean Difference Study or subgroup Higher PUFA Lower PUFA Weight Ν Mean(SD) Ν Mean(SD) IV,Random,95% CI IV,Random,95% CI -0.01 [-0.12, 0.10] Mendis 2001 26 0.26 (0.1981) 28 0.27 (0.2063) 2.3 % 0.07 [-0.18, 0.32] Mita 2007 30 1.51 (0.59) 30 1.44 (0.37) 0.4 % Nye 1990 12 1.38 (0.43) 12 1.45 (0.38) 0.2 % -0.07 [-0.39, 0.25] Vijayakumar 2014 94 1.15 (0.42) 96 2.5 % 0.03 [-0.07, 0.13] 1.12 (0.28) WELCOME 2015 2.5 % 0.0 [-0.10, 0.10] 47 1.1 (0.3) 48 1.1 (0.2) Subtotal (95% CI) 950 920 45.0 % -0.01 [-0.03, 0.01] Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.00$, df = 8 (P = 0.93); $I^2 = 0.0\%$ Test for overall effect: Z = 0.84 (P = 0.40) **Total (95% CI)** 2310 100.0 % -0.01 [-0.02, 0.01] 2364 Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.25$, df = 19 (P = 0.95); $I^2 = 0.0\%$ Test for overall effect: Z = 0.81 (P = 0.42) Test for subgroup differences: $Chi^2 = 0.25$, df = 2 (P = 0.88), $I^2 = 0.0\%$ -0.2 -0.I 0.1 Favours higher PUFA Favours lower PUFA

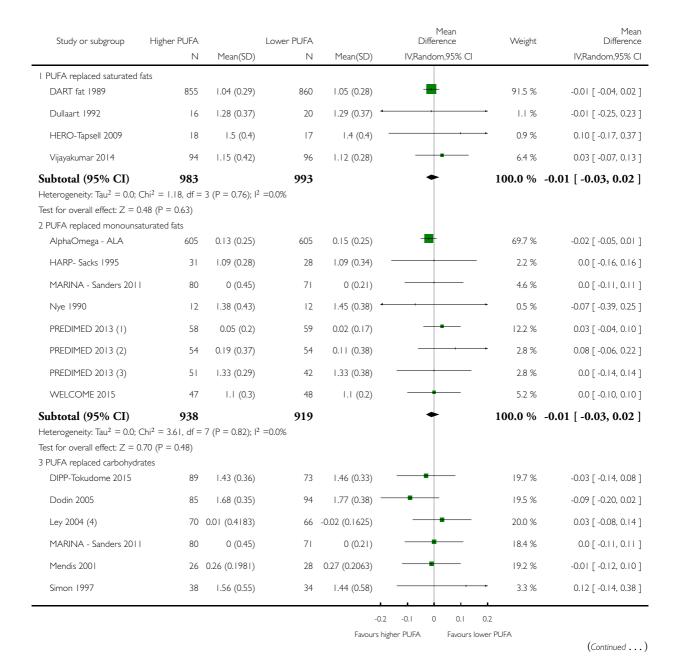
- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016

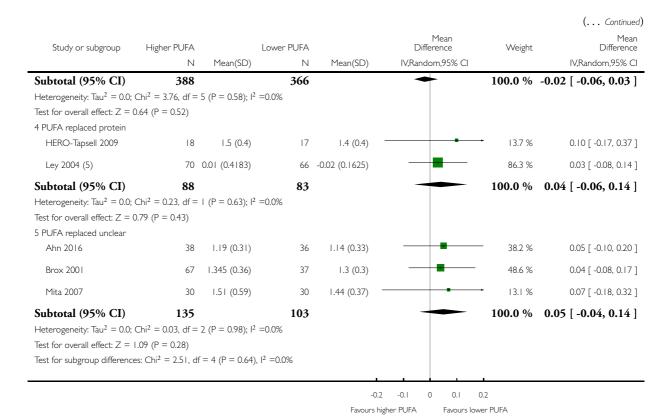
Analysis 3.59. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 59 HDL, mmoL/L - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 59 HDL, mmoL/L - subgroup by replacement



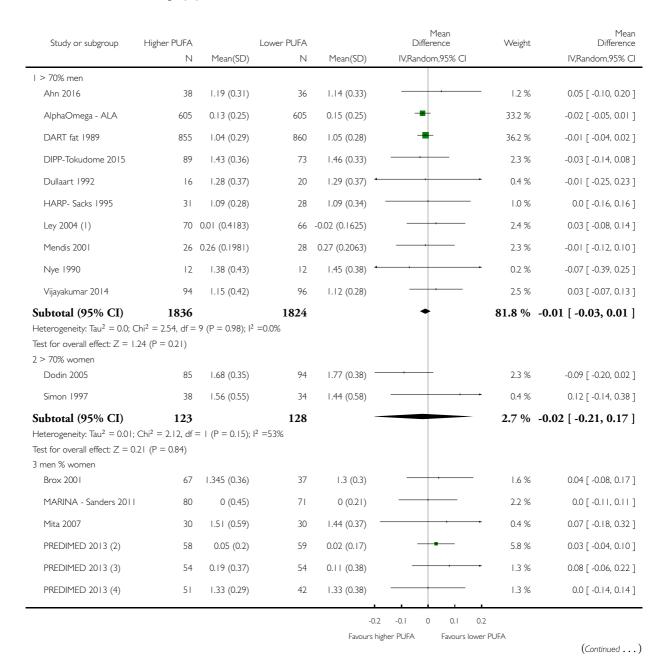


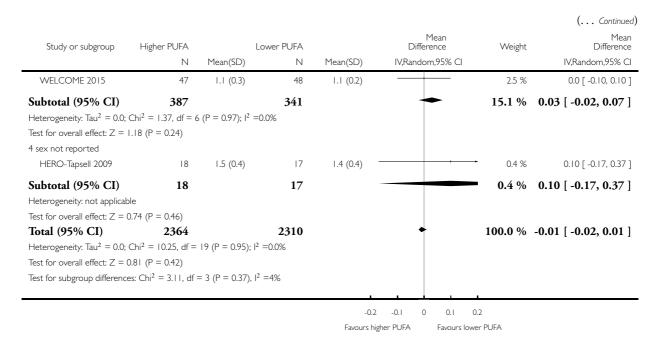
- (I) Damasceno 2013, Barcelona North subcohort, I year data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Change data
- (5) Change data

Analysis 3.60. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 60 HDL, mmoL/L - subgroup by sex.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 60 HDL, mmoL/L - subgroup by sex



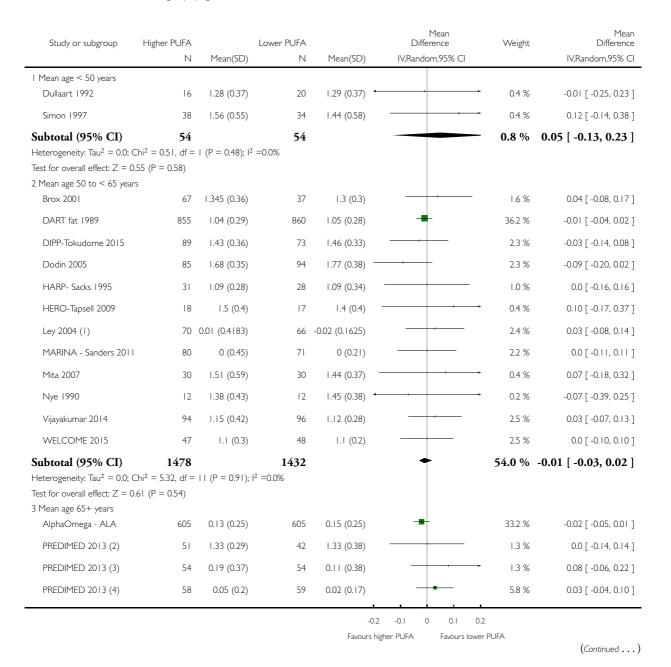


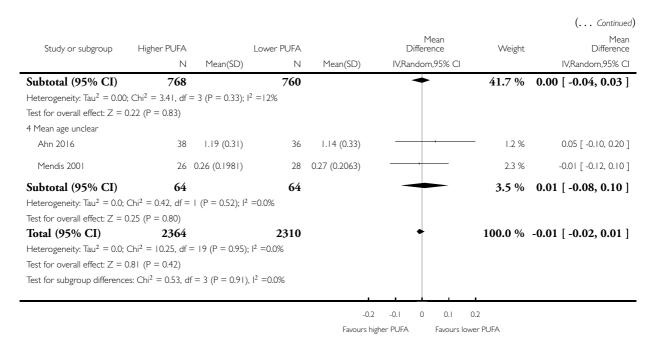
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.61. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 61 HDL, mmoL/L - subgroup by age.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 61 HDL, mmoL/L - subgroup by age



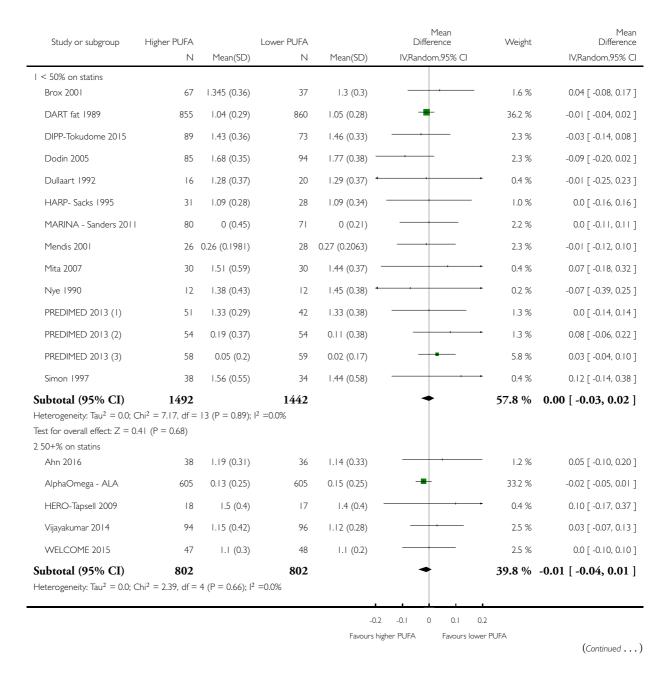


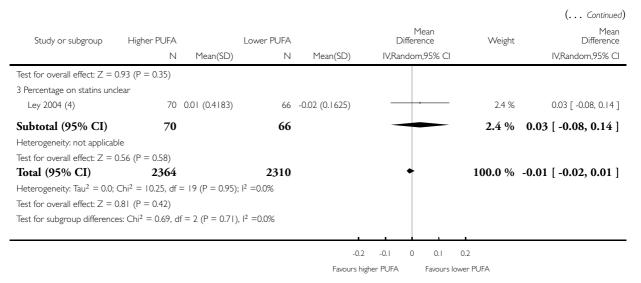
- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.62. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 62 HDL, mmoL/L - subgroup by statin use.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 62 HDL, mmoL/L - subgroup by statin use



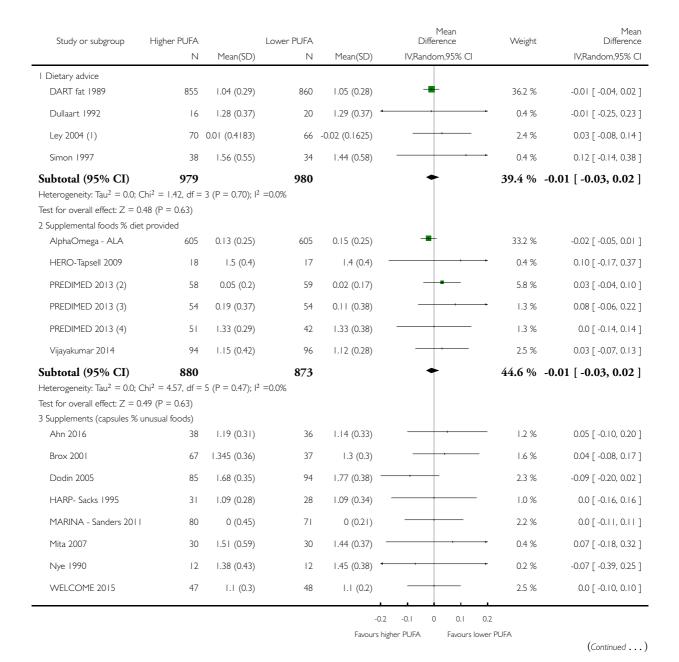


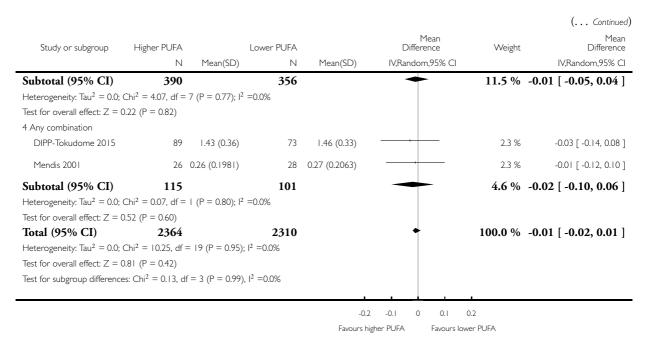
- (1) Fernandez-Real 2012, Reus subcohort, 2 year data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Change data

Analysis 3.63. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 63 HDL, mmoL/L - subgroup by intervention type.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 63 HDL, mmoL/L - subgroup by intervention type





- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data

Analysis 3.64. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 64 Serum LOW DENSITY LIPOPROTEIN (LDL, mmoL/L).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 64 Serum LOW DENSITY LIPOPROTEIN (LDL, mmoL/L)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		2.8 %	0.16 [-0.26, 0.58]
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)	+	14.5 %	0.01 [-0.07, 0.09]
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [-0.39, 0.01]
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)	-	3.7 %	0.25 [-0.11, 0.61]
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	•	2.2 %	-0.10 [-0.59, 0.39]
Ley 2004 (I)	70	-0.02 (1.255)	66	-0.18 (0.7312)		3.9 %	0.16 [-0.18, 0.50]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		7.2 %	0.0 [-0.22, 0.22]
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	•	2.6 %	-0.07 [-0.51, 0.37]
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)	-	11.3 %	0.09 [-0.04, 0.23]
PREDIMED 2013 (2)	54	-1.14 (0.95)	54	-0.62 (0.92)		3.7 %	-0.52 [-0.87, -0.17]
PREDIMED 2013 (3)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [-0.30, 0.26]
PREDIMED 2013 (4)	51	3.26 (0.86)	42	3.07 (0.7)		4.4 %	0.19 [-0.13, 0.51]
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)	•	1.2 %	0.12 [-0.56, 0.80]
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)	- 	2.8 %	0.30 [-0.12, 0.72]
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [-0.22, 0.16]
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [-0.25, -0.05]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [-0.34, 0.34]
Total (95% CI) eterogeneity: $Tau^2 = 0.01$; CI est for overall effect: $Z = 0.33$ est for subgroup differences: I	B (P = 0.74)	`	1668 3); I ² =44%		+	100.0 %	-0.01 [-0.09, 0.06]

Favours higher PUFA

Favours lower PUFA

- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) change from baseline

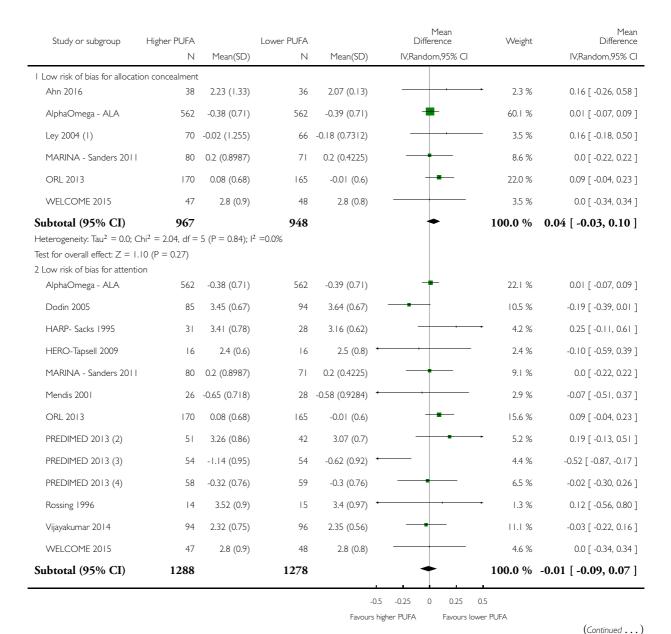
⁽I) Change data

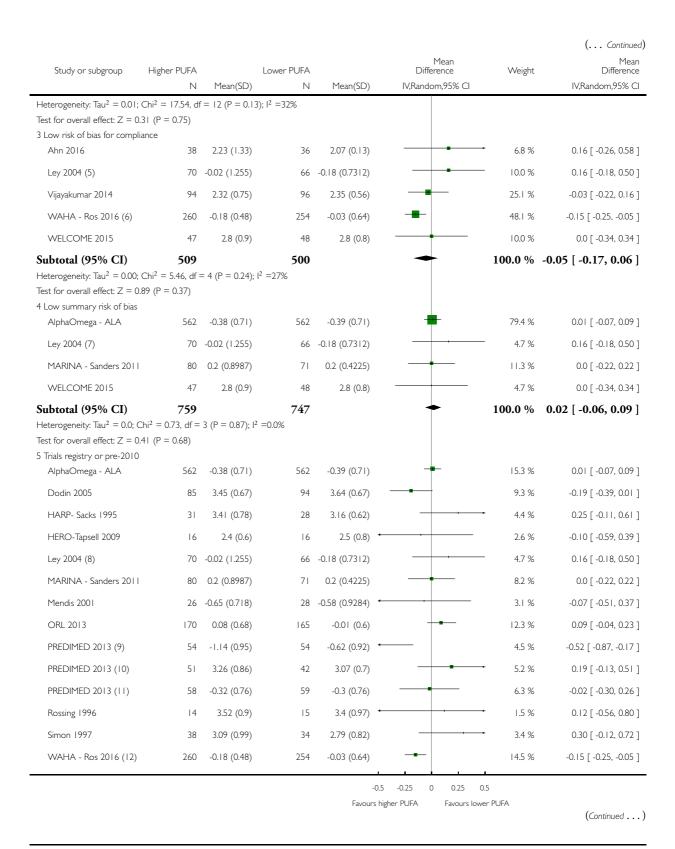
Analysis 3.65. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 65 LDL, mmoL/L - SA.

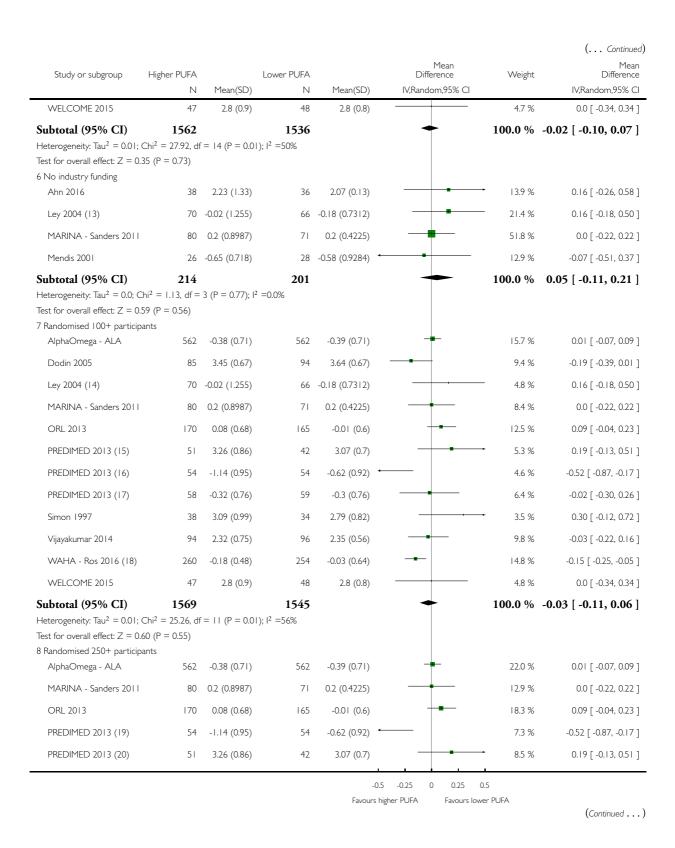
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

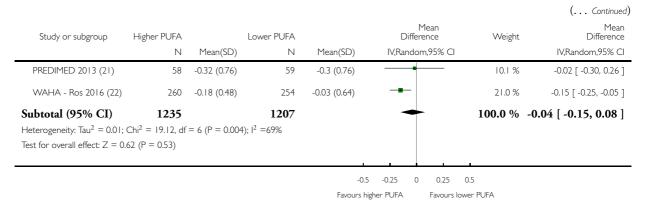
Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 65 LDL, mmoL/L - SA









- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Change data
- (6) change from baseline
- (7) Change data
- (8) Change data
- (9) Barcelona hospital cohort at 5 years, Casa 2016
- (10) Fernandez-Real 2012, Reus subcohort, 2 year data
- (11) Damasceno 2013, Barcelona North subcohort, 1 year data
- (12) change from baseline
- (13) Change data
- (14) Change data
- (15) Fernandez-Real 2012, Reus subcohort, 2 year data
- (16) Barcelona hospital cohort at 5 years, Casa 2016
- (17) Damasceno 2013, Barcelona North subcohort, I year data
- (18) change from baseline
- (19) Barcelona hospital cohort at 5 years, Casa 2016
- (20) Fernandez-Real 2012, Reus subcohort, 2 year data
- (21) Damasceno 2013, Barcelona North subcohort, I year data
- (22) change from baseline

Analysis 3.66. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 66 LDL, mmoL/L - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 66 LDL, mmoL/L - SA fixed-effect

subgroup Higher PUF	Ą	Lower PUFA		Mean Difference	Weight	Mear Difference
1	N Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% C
3	8 2.23 (1.33)	36	2.07 (0.13)		÷ 1.2 %	0.16 [-0.26, 0.58]
ga - ALA 56	2 -0.38 (0.71)	562	-0.39 (0.71)	+	31.8 %	0.01 [-0.07, 0.09]
5 8	5 3.45 (0.67)	94	3.64 (0.67)		5.7 %	-0.19 [-0.39, 0.01]
:ks 1995 3	3.41 (0.78)	28	3.16 (0.62)	 	÷ 1.7 %	0.25 [-0.11, 0.61]
sell 2009	6 2.4 (0.6)	16	2.5 (0.8)		0.9 %	-0.10 [-0.59, 0.39]
1) 7	0 -0.02 (1.255)	66	-0.18 (0.7312)		1.9 %	0.16 [-0.18, 0.50]
Sanders 2011 8	0.2 (0.8987)	71	0.2 (0.4225)		4.5 %	0.0 [-0.22, 0.22]
01 2	6 -0.65 (0.718)	28	-0.58 (0.9284)		1.1 %	-0.07 [-0.51, 0.37]
17	0.08 (0.68)	165	-0.01 (0.6)		11.7 %	0.09 [-0.04, 0.23]
2013 (2) 5	4 -1.14 (0.95)	54	-0.62 (0.92)	-	1.8 %	-0.52 [-0.87, -0.17]
2013 (3) 5	3.26 (0.86)	42	3.07 (0.7)		÷ 2.2 %	0.19 [-0.13, 0.51]
2013 (4) 5	8 -0.32 (0.76)	59	-0.3 (0.76)		2.9 %	-0.02 [-0.30, 0.26
96 I	4 3.52 (0.9)	15	3.4 (0.97)	+ +	• 0.5 %	0.12 [-0.56, 0.80
7 3	3.09 (0.99)	34	2.79 (0.82)		÷ 1.3 %	0.30 [-0.12, 0.72
ur 2014 9	4 2.32 (0.75)	96	2.35 (0.56)		6.2 %	-0.03 [-0.22, 0.16
Ros 2016 (5) 26	0 -0.18 (0.48)	254	-0.03 (0.64)	-	22.9 %	-0.15 [-0.25, -0.05
E 2015 4	7 2.8 (0.9)	48	2.8 (0.8)		1.9 %	0.0 [-0.34, 0.34]
6 CI) 169	í	1668		•	100.0 %	-0.03 [-0.07, 0.02]
$V: Chi^2 = 28.67, df = 16 (P = 16)$	0.03); I ² =44%					
II effect: $Z = 1.11 (P = 0.27)$						
oup differences: Not applicat	le					

Favours higher PUFA

Favours lower PUFA

⁽I) Change data

⁽²⁾ Barcelona hospital cohort at 5 years, Casa 2016

⁽³⁾ Fernandez-Real 2012, Reus subcohort, 2 year data

⁽⁴⁾ Damasceno 2013, Barcelona North subcohort, I year data

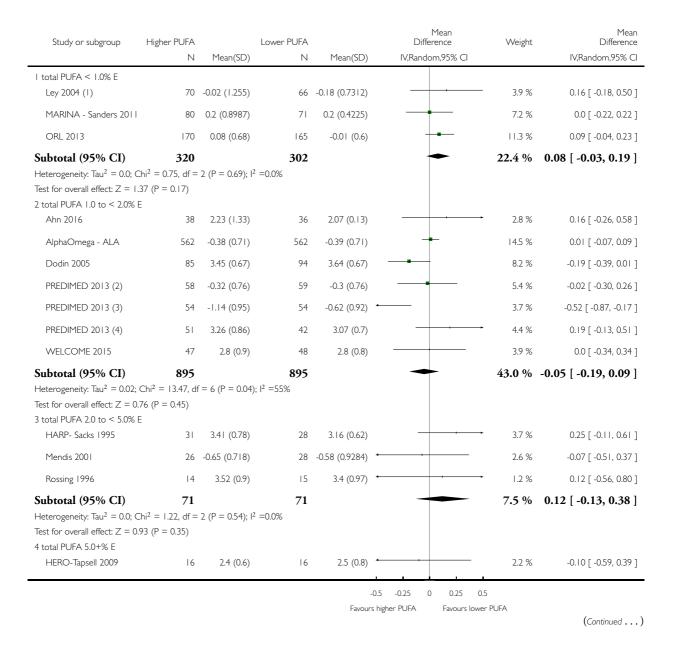
⁽⁵⁾ change from baseline

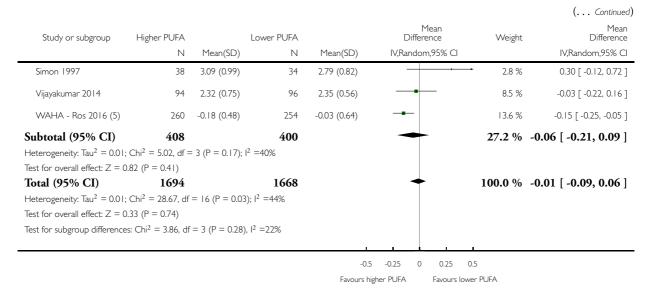
Analysis 3.67. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 67 LDL, mmoL/L - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 67 LDL, mmoL/L - subgroup by PUFA dose





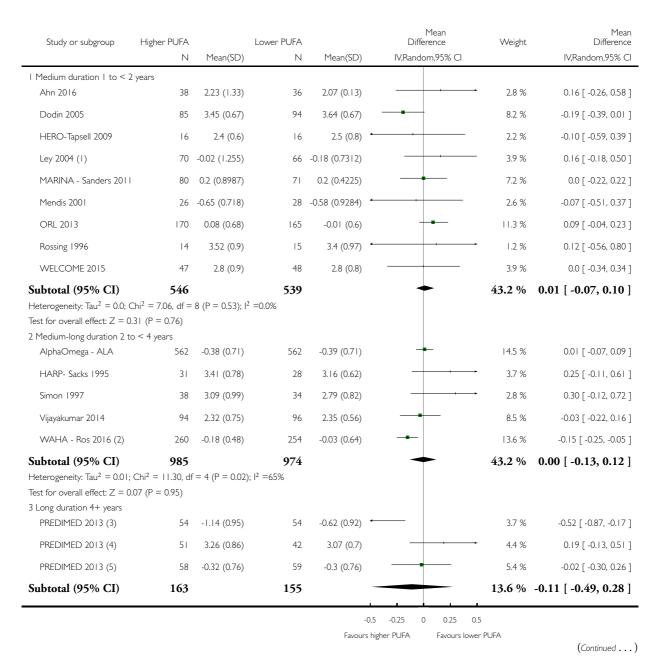
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) change from baseline

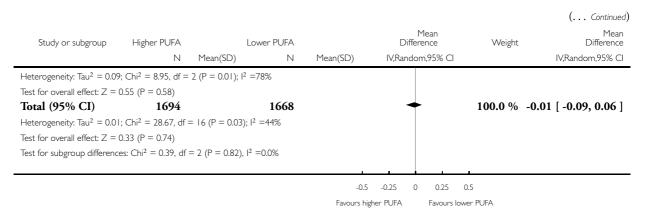
Analysis 3.68. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 68 LDL, mmoL/L - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 68 LDL, mmoL/L - subgroup by duration





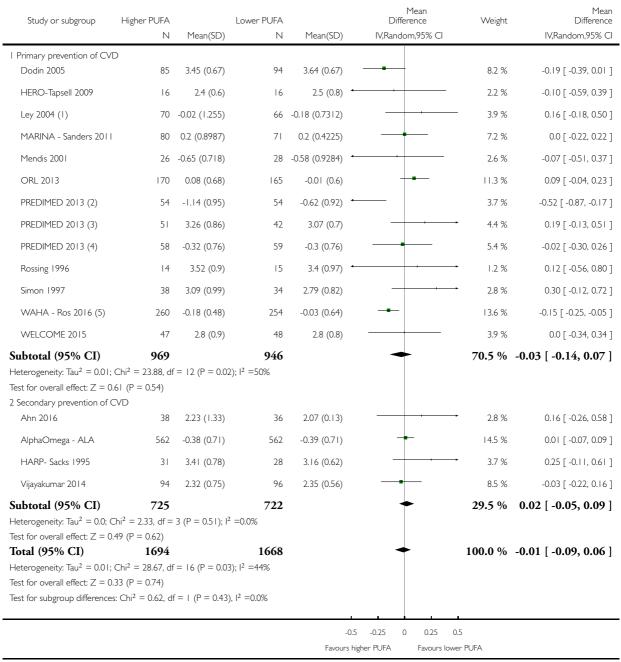
- (I) Change data
- (2) change from baseline
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data

Analysis 3.69. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 69 LDL, mmoL/L - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 69 LDL, mmoL/L - subgroup by primary or secondary prevention



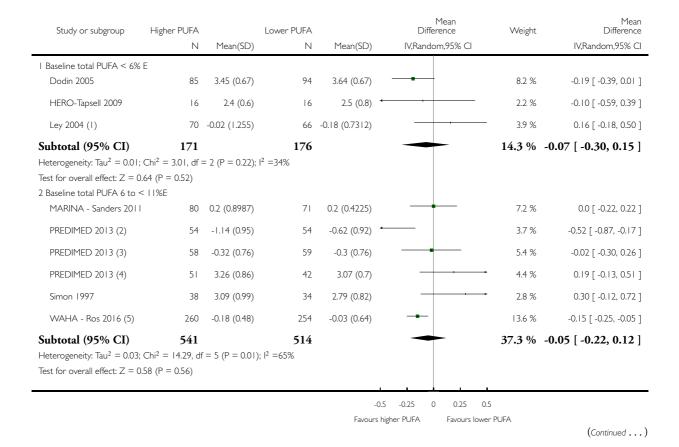
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) change from baseline

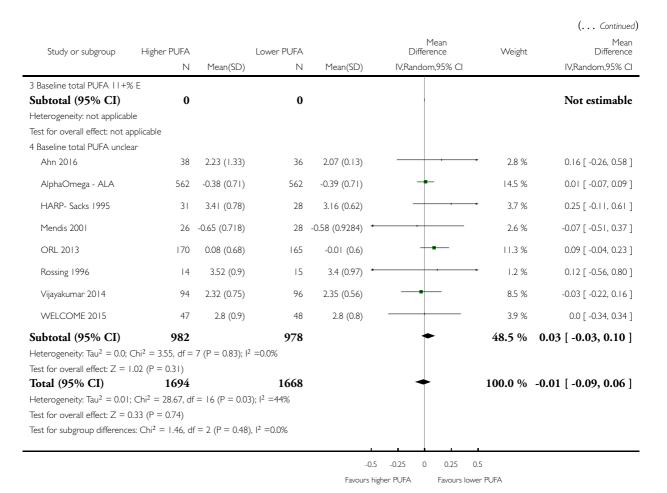
Analysis 3.70. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 70 LDL, mmoL/L - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 70 LDL, mmoL/L - subgroup by baseline PUFA dose



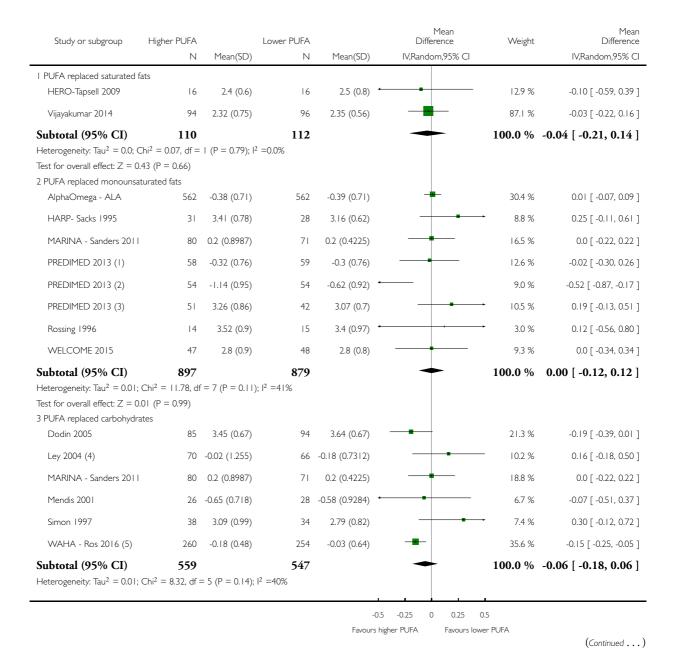


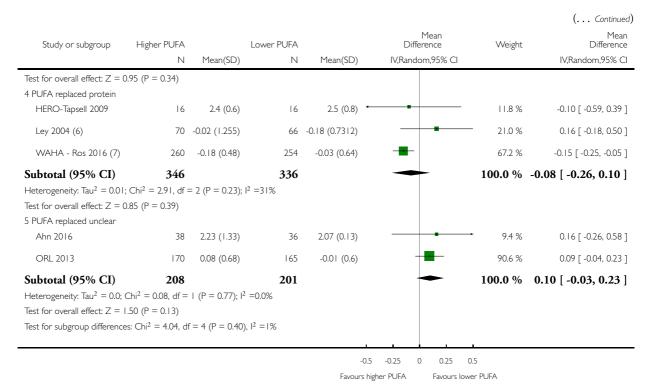
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) change from baseline

Analysis 3.71. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 71 LDL, mmoL/L - subgroup by replacement.

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 71 LDL, mmoL/L - subgroup by replacement





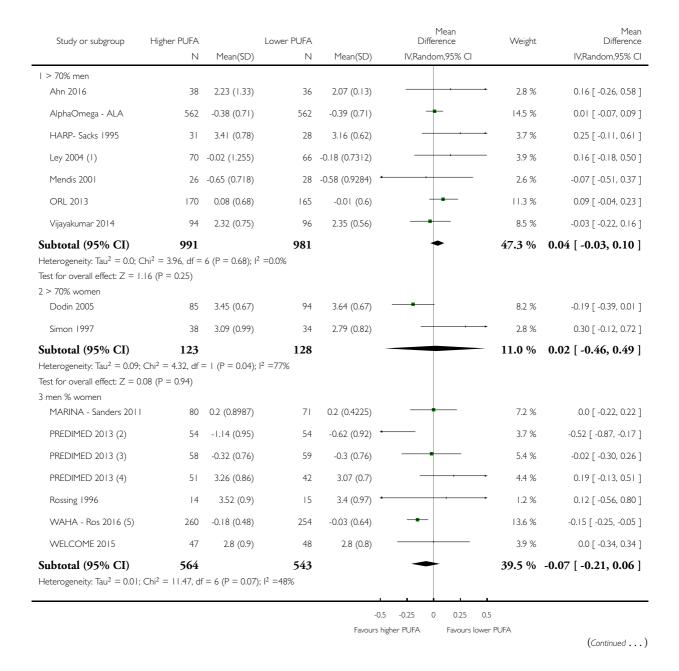
- (I) Damasceno 2013, Barcelona North subcohort, I year data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Change data
- (5) change from baseline
- (6) Change data
- (7) change from baseline

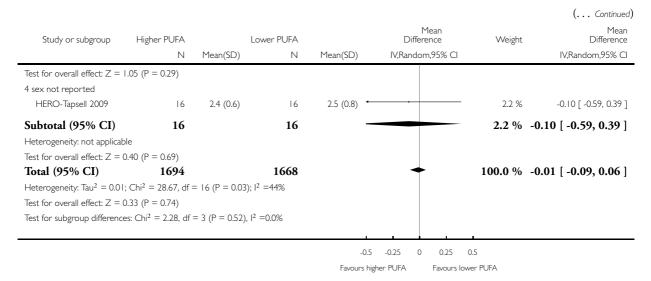
Analysis 3.72. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 72 LDL, mmoL/L - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 72 LDL, mmoL/L - subgroup by sex





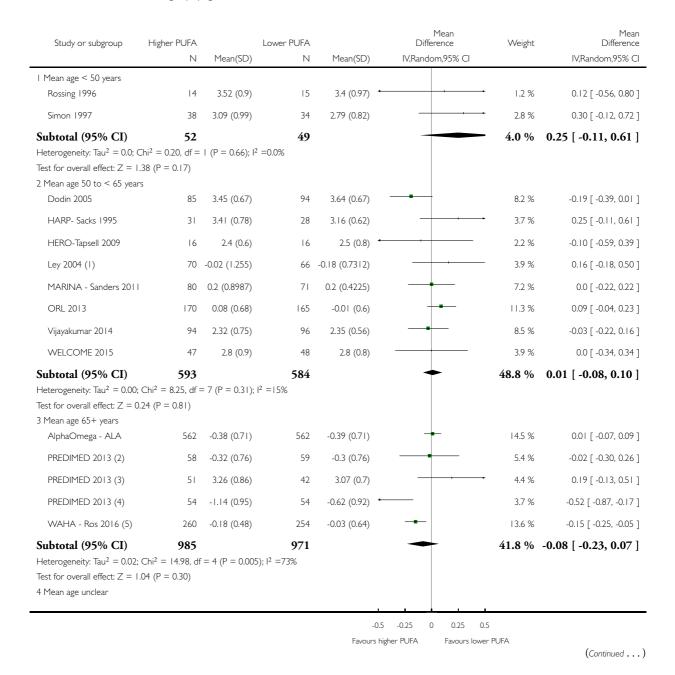
- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) change from baseline

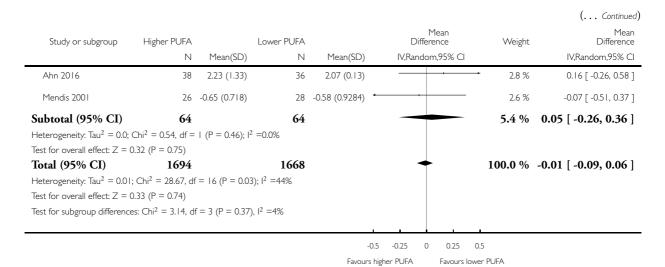
Analysis 3.73. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 73 LDL, mmoL/L - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 73 LDL, mmoL/L - subgroup by age





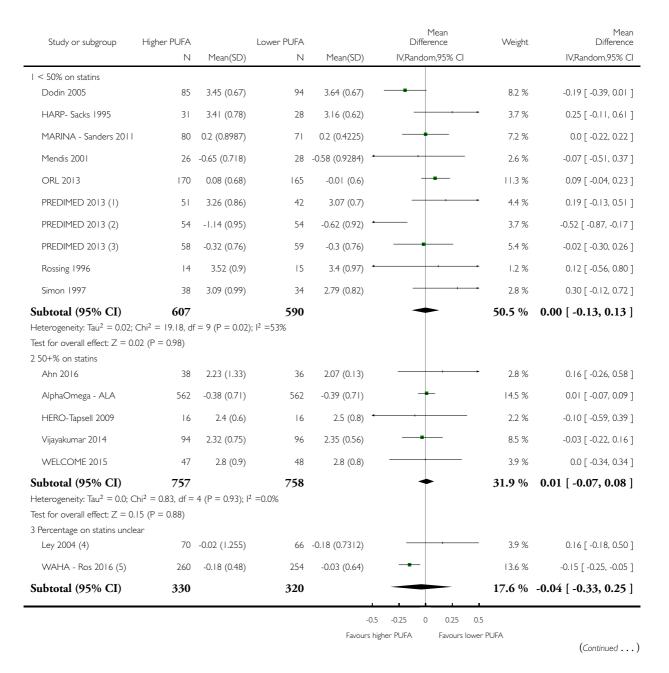
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) change from baseline

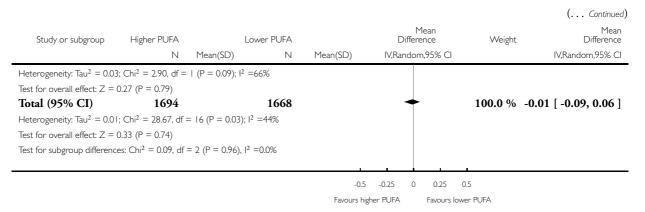
Analysis 3.74. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 74 LDL, mmoL/L - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 74 LDL, mmoL/L - subgroup by statin use





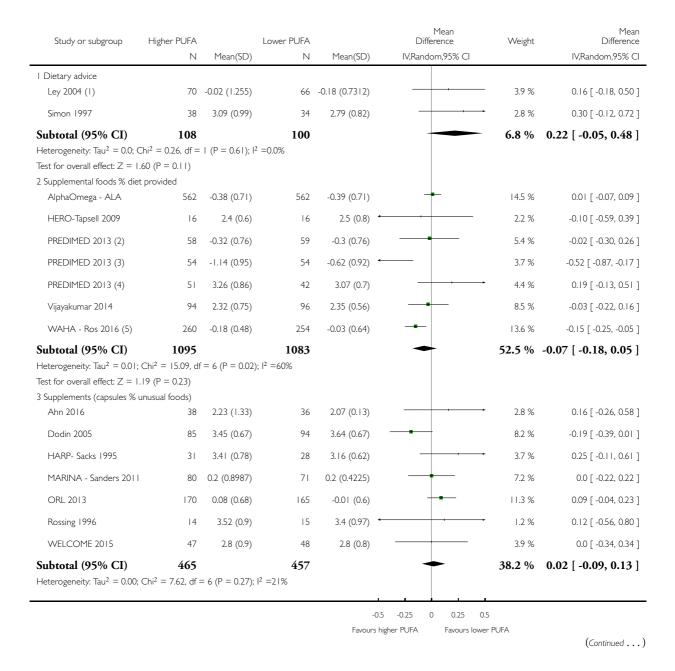
- (I) Fernandez-Real 2012, Reus subcohort, 2 year data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Damasceno 2013, Barcelona North subcohort, I year data
- (4) Change data
- (5) change from baseline

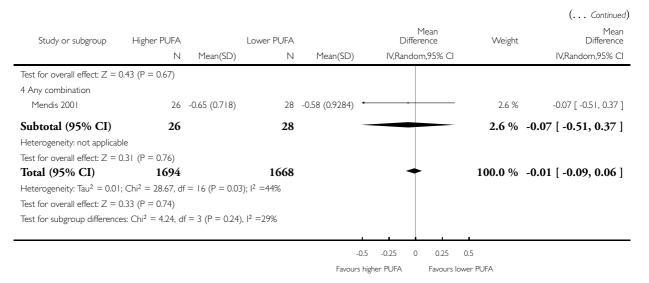
Analysis 3.75. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 75 LDL, mmoL/L - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 75 LDL, mmoL/L - subgroup by intervention type





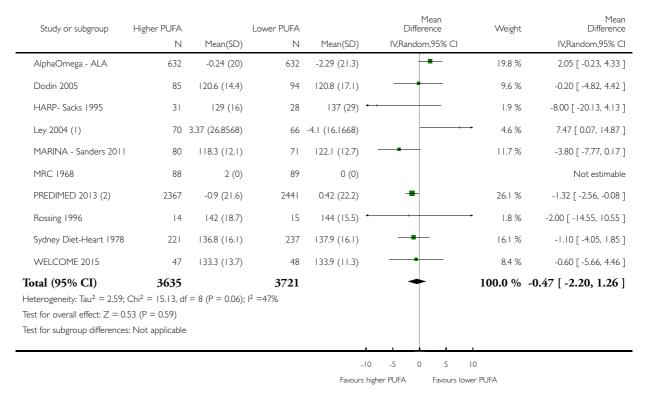
- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) change from baseline

Analysis 4.1. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome I SYSTOLIC BLOOD PRESSURE (sBP, mmHg).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: I SYSTOLIC BLOOD PRESSURE (sBP, mmHg)



(I) change data

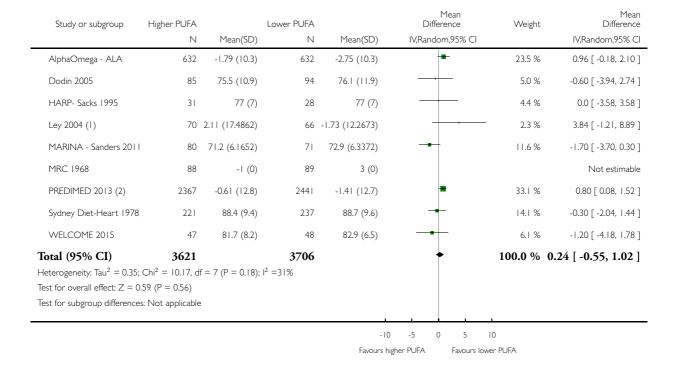
(2) Toledo BMC Med 2013

Analysis 4.2. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome 2 DIASTOLIC BLOOD PRESSURE (dBP, mmHg).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: 2 DIASTOLIC BLOOD PRESSURE (dBP, mmHg)



⁽I) Change data

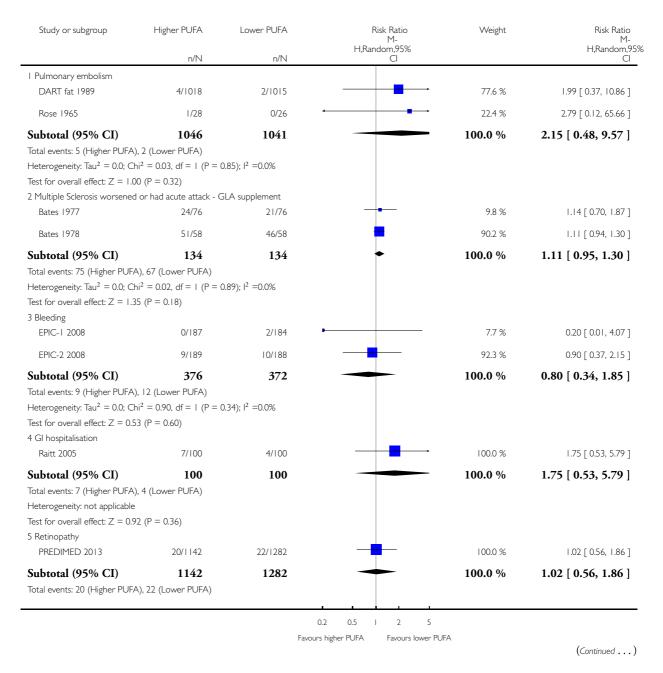
⁽²⁾ Toledo BMC MED 2013

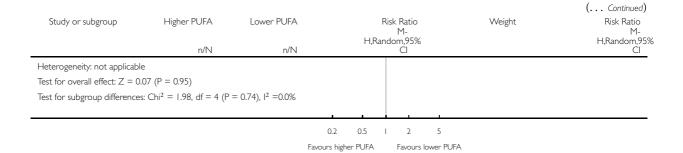
Analysis 4.3. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome 3 SERIOUS ADVERSE EVENTS (SAEs).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: 3 SERIOUS ADVERSE EVENTS (SAEs)



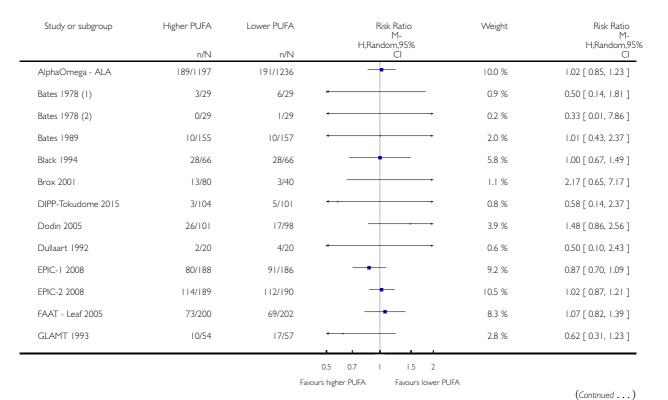


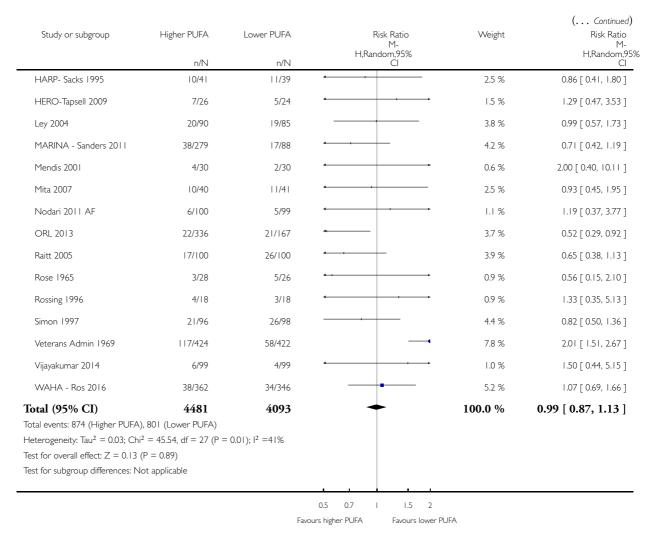
Analysis 4.4. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome 4 DROPOUTS.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: 4 DROPOUTS





⁽I) Arms C vs D, both given spread

ADDITIONAL TABLES

Table 1. Risk of bias assessment - detailed assessment methods

Risk of bias element	Criteria for low risk of bias	Criteria for unclear	Criteria for high risk of bias
Selection bias: random sequence generation	to generate the allocation se-	The trial authors have not described their method in sufficient detail for the assessment of whether it would produce	assessed as not truly random, and may not produce compara-

⁽²⁾ Arms A vs B, both given capsules

Table 1. Risk of bias assessment - detailed assessment methods (Continued)

	low an assessment of whether it should produce comparable groups. For example "the randomisation sequence was computer-generated". We allowed that a good method of randomisation was strongly implied if the trial authors discussed stratification and/or blocking. Therefore, if they were not explicit about their randomisation method but did describe stratification or blocking we assessed this as low risk	comparable groups. For example, the trial authors state "the trial was randomised" and provide no further information	
Selection bias: allocation concealment	The trial authors needed to have described the method used to conceal allocation sequence in sufficient detail to determine whether the allocations could have been foreseen in advance of, or during, enrolment. Good methods included putting allocation codes in opaque, sealed envelopes (ideally prepared by someone outside the treatment or assessment teams and sequentially numbered), using a telephone allocation system after the participants had consented to participate or providing a random number that links to a specific set of capsules prepared and distributed centrally or by an arms-length pharmacist	The authors gave insufficient detail as to method.	The allocation was known in advance of participants consenting to take part in the trial
Performance bias: blinding of participants and personnel		Insufficient methodological details were provided e.g. "the trial was blinded."	

Table 1. Risk of bias assessment - detailed assessment methods (Continued)

	" However if the trial authors did not provide information on whether the blinding was ef-		
	fective, but sufficient detail was given on a good method of blinding, then it was assumed that the blinding was effective and the risk of bias was low		
Detection bias: blinding of outcome assessment	Trial authors needed to have described measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective. For example, the authors could say "the outcome assessors had no knowledge of the group allocation, and both the intervention and placebo capsules looked and tasted the same so the self-assessment scales were also blinded." However if the trial authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding of the assessors, then it was assumed that the blinding was effective and the risk of bias is low. All biochemical assessment (lipids, glucose, CRP, insulin, PSA etc.) were considered at low risk of detection bias if outcome assessor blinding or double blinding was stated	Insufficient methodological details were provided e.g. "the trial was blinded."	The trial was unblinded or blinding was broken, e.g. for a self-assessment measure "the capsules were visually identical but the participants reported a strong fishy flavour in the intervention group only." (Because the level of blinding could vary by outcome assessment of risk of bias was based on blinding of the review's primary outcome(s). Where primary outcomes had different assessments we opted for the higher risk of bias but noted that risk of bias was lower for other outcomes
Attrition bias: incomplete outcome data	The trial authors needed to describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. They needed to report the number of attrition/exclusions, the numbers in each group at each time point, reasons for attri-	The trial authors didn't state reasons for attrition/exclusion, or were unclear about the numbers lost to attrition/exclusion in each trial arm	The trial authors demonstrated a substantial difference in the rates of attrition/ exclusions between the trial arms and/or > 20% of the baseline sample was lost over a year (> 10% over 6 months)

Table 1. Risk of bias assessment - detailed assessment methods (Continued)

	tion/exclusion and any re-inclusions in analyses. Ideally, they would report how they imputed any missing data e.g. last observation carried forward. There needed to be a reasonable balance of attrition/exclusions between trial arms and ≤ 20% of the sample should be lost over a year		
Reporting bias: selective outcome reporting	published their trial protocol or trials registry entry before the end of the trial's recruitment	No trial protocol or trials registry entry was found, it was registered retrospectively, or the dates of registration and participant recruitment were unclear	The trial authors did not report at least one primary or secondary outcome listed in the protocol/registry entry OR the results paper(s) reported a primary outcome that was not listed at all in the protocol or not listed as a primary outcome in the protocol
Other sources of bias: Attention bias	The trial authors needed to have reported that participants in all trial arms received the same amount of attention and time from researchers and clinical teams. For example, "All participants attended the clinic for a baseline assessment which took 2 hours. They were then followed with monthly telephone calls, and finally attended for a 6 month assessment at the clinic which took 1 hour." If the trial only differed by the content of the capsules, and the assessment schedule was not stated to differ between the two arms, it was assumed to be at low risk	The trial authors did not state the attention each arm received	-
Other sources of bias: limited compliance	The higher PUFA arm had to demonstrate an increase in PUFA fats over control in a body biomarker (total PUFA had to be assessed by at least LA plus one or more further com-	Biomarker data not reported or not in a way that could be inter- preted. Where lipid biomarker and TC contradicted each other we chose unclear	Measures of compliance were reported but did not suggest higher total PUFA in the appro- priate arm

Table 1. Risk of bias assessment - detailed assessment methods (Continued)

	ponents of PUFA), or greater reduction in TC in the higher PUFA arm	
Other sources of bias: other	In the absence of any additional issues this item was coded "low risk of bias"	If fraud concerns had been raised and the paper had been withdrawn, or the trial author had been found guilty of fraud by a legal or medical entity the paper was excluded from the review. However if fraud concerns were raised, but the journal had not withdrawn the paper, and the trial author had not been formally sanctioned; then the trial was included in the review, but concerns were raised here, and the risk of bias for this item was high

LA: linoleic acid; PUFA: polyunsaturated fatty acids; TC: total cholesterol

APPENDICES

Appendix I. Searches run for this review, to 27 April 2017

These searches have each been run from database inception, then de-duplicated with each other. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter, and for Embase, terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* have been applied (Lefebvre 2011).

CENTRAL

- #1 MeSH descriptor: [Fatty Acids, Essential] explode all trees
- #2 MeSH descriptor: [Fatty Acids, Unsaturated] this term only
- #3 ((polyunsaturat* or poly-unsaturat*) near/3 fat*)
- #4 (poly* adj4 unsat* near/4 fatty acid*)
- #5 PUFA
- #6 MeSH descriptor: [Fatty Acids, Omega-6] explode all trees
- #7 omega-6
- #8 (n-6 near/4 acid*) or ("n 6" near/4 acid*)
- #9 linoleic acid*
- #10 MeSH descriptor: [Corn Oil] this term only
- #11 MeSH descriptor: [Cottonseed Oil] this term only
- #12 MeSH descriptor: [Olive Oil] this term only
- #13 MeSH descriptor: [Safflower Oil] this term only
- #14 MeSH descriptor: [Sesame Oil] this term only
- #15 MeSH descriptor: [Soybean Oil] this term only

- #16 ((corn or maize or mazola) near/4 oil*)
- #17 (cottonseed* or (cotton next seed*))
- #18 (olive near/4 oil*)
- #19 (safflower near/4 oil*)
- #20 (sesame near/4 oil*)
- #21 ((soy bean or soybean) near/4 (oil* or fat*))
- #22 (so?a near/4 oil*)
- #23 so?aoil*
- #24 (soy near/4 oil*)
- #25 (sunflower near/4 oil*)
- #26 helianth*
- #27 (grapeseed near/4 oil*)
- #28 (canola near/4 oil*)
- #29 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28

MEDLINE Ovid

- 1. exp fatty acids, essential/
- 2. fatty acids, unsaturated/
- 3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.
- 4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.
- 5. PUFA.ti,ab.
- 6. exp fatty acids, omega-6/
- 7. omega-6.ti,ab.
- 8. (n-6 adj4 acid*).ti,ab.
- 9. linoleic acid*.ti.ab.
- 10. corn oil/ or cottonseed oil/ or olive oil/ or safflower oil/ or sesame oil/ or soybean oil/
- 11. ((corn or maize or mazola) adj4 oil*).ti,ab.
- 12. (cottonseed* or (cotton adj seed*)).ti,ab.
- 13. (olive adj4 oil*).ti,ab.
- 14. (safflower adj4 oil*).ti,ab.
- 15. (sesame adj4 oil*).ti,ab.
- 16. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.
- 17. (so?a adj4 oil*).ti,ab.
- 18. so?aoil*.ti,ab.
- 19. (soy adj4 oil*).ti,ab.
- 20. (sunflower adj4 oil*).ti,ab.
- 21. helianth*.ti,ab.
- 22. (grapeseed adj4 oil*).ti,ab.
- 23. (canola adj4 oil*).ti,ab.
- 24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
- 25. randomized controlled trial.pt.
- 26. controlled clinical trial.pt.
- 27. randomized.ab.
- 28. placebo.ab.
- 29. clinical trials as topic.sh.
- 30. randomly.ab.
- 31. trial.ti.
- 32. 25 or 26 or 27 or 28 or 29 or 30 or 31
- 33. exp animals/ not humans.sh.
- 34. 32 not 33
- 35. 24 and 34

Embase Ovid

1. exp essential fatty acid/

- 2. unsaturated fatty acid/ or docosapentaenoic acid/ or omega 6 fatty acid/ or polyunsaturated fatty acid/
- 3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.
- 4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.
- 5. PUFA.ti,ab.
- 6. omega-6.ti,ab.
- 7. (n-6 adj4 acid*).ti,ab.
- 8. linoleic acid*.ti,ab.
- 9. edible oil/ or canola oil/ or corn oil/ or cotton seed oil/ or olive oil/ or safflower oil/ or safflower oil plus soybean oil/ or sesame seed oil/ or soybean oil/ or sunflower oil/
- 10. ((corn or maize or mazola) adj4 oil*).ti,ab.
- 11. (cottonseed* or (cotton adj seed*)).ti,ab.
- 12. (olive adj4 oil*).ti,ab.
- 13. (safflower adj4 oil*).ti,ab.
- 14. (sesame adj4 oil*).ti,ab.
- 15. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.
- 16. (so?a adj4 oil*).ti,ab.
- 17. so?aoil*.ti,ab.
- 18. (soy adj4 oil*).ti,ab.
- 19. (sunflower adj4 oil*).ti,ab.
- 20. helianth*.ti,ab.
- 21. (grapeseed adj4 oil*).ti,ab.
- 22. (canola adj4 oil*).ti,ab.
- 23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
- 24. double blind procedure/
- 25. single blind procedure/
- 26. randomized controlled trial/
- 27. ((double* or single*) adj blind*).ti,ab.
- 28. (random* or placebo*).ti,ab.
- 29. 24 or 25 or 26 or 27 or 28
- 30. (animal/ or nonhuman/) not human/
- 31. 29 not 30
- 32. 23 and 31

Appendix 2. Searches run for the allied review, to 27 April 2017

The searches for the omega-3 review (Abdelhamid 2018) were last run in 20 February 2002. We have updated the search strategies and have now re-run the searches to identify any records added to the databases since the last search. We applied date limits to the terms from the original strategies so that only new records would be found, but have not applied date limits to the newly added terms. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter, and for Embase, we have applied terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

CENTRAL

- #1 MeSH descriptor: [Fish Oils] explode all trees
- #2 MeSH descriptor: [Linseed Oil] this term only
- #3 MeSH descriptor: [Linolenic Acids] this term only
- #4 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
- #5 (fish near/3 oil*)
- #6 (oil* near/3 (cod* or marin*))
- #7 (omega-3 or omega3 or (omega* near/5 fat*))
- #8 eicosapentaen*
- #9 docosahexaen*
- #10 (oil* near/3 (flax* or rapeseed* or canola*))
- #11 (Linolen* or alpha-linolen* or alphalinolen*)

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#12 (perilla* or linseed* or maxepa*)
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- #13 (oil* near/3 (rape or colza))
- #14 (marin* near/3 lipid*)
- #15 (naudicelle* or herring* or sild)
- #16 (clupe* near/3 hareng*)
- #17 (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*)
- #18 (salmo* near/3 trut*)
- #19 (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish)
- #20 (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus*)
- #21 (crab or crabs or (cancer pagarus))
- #22 (DHA or EPA)
- #23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #
- 20 or #21 or #22 Publication Year from 2002 to 2016
- #24 MeSH descriptor: [Salmoniformes] explode all trees
- #25 MeSH descriptor: [Tuna] this term only
- #26 MeSH descriptor: [alpha-Linolenic Acid] this term only
- #27 MeSH descriptor: [Flax] this term only
- #28 (fish near/3 (diet* or capsul* or nutrit* or supplement*))
- #29 (icosapentaen* or docosapentaen*)
- #30 (oil* near/3 (purslane or mustard* or candlenut* or stillingia or walnut*))
- #31 (laks or lax)
- #32 (ALA or DPA)
- #33 (algal near oil*)
- #34 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
- #35 #23 or #34

MEDLINE Ovid

- 1. exp Fish Oils/
- 2. Linseed Oil/
- 3. linolenic acids/ or alpha-linolenic acid/
- 4. Flax/
- 5. exp Fatty Acids, Omega-3/
- 6. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.
- 7. (oil* adj3 (cod* or marin*)).ti,ab.
- 8. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.
- 9. eicosapentaen*.ti,ab.
- 10. docosahexaen*.ti,ab.
- 11. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.
- 12. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.
- 13. (perilla* or linseed* or maxepa*).ti,ab.
- 14. (oil* adj3 (rape or colza)).ti,ab.
- 15. (marin* adj3 lipid*).ti,ab.
- 16. (naudicelle* or herring* or sild).ti,ab.
- 17. (clupe* adj3 hareng*).ti,ab.
- 18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.
- 19. (salmo* adj3 trut*).ti,ab.
- 20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.
- 21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.
- 22. (crab or crabs or cancer pagarus).ti,ab.
- $23.\ 1\ or\ 2\ or\ 3\ or\ 4\ or\ 5\ or\ 6\ or\ 7\ or\ 8\ or\ 9\ or\ 10\ or\ 11\ or\ 12\ or\ 13\ or\ 14\ or\ 15\ or\ 16\ or\ 17\ or\ 18\ or\ 19\ or\ 20\ or\ 21\ or\ 22\ or\ 22\ or\ 23\ or\ 24\ or\ 25\ or\$
- 24. randomized controlled trial.pt.
- 25. controlled clinical trial.pt.
- 26. randomized.ab.
- 27. placebo.ab.

- 28. clinical trials as topic.sh.
- 29. randomly.ab.
- 30. trial.ti.
- 31. 24 or 25 or 26 or 27 or 28 or 29 or 30
- 32. exp animals/ not humans.sh.
- 33. 31 not 32
- 34. 23 and 33
- 35. limit 34 to ed=20020201-20160721
- 36. exp salmoniformes/ or tuna/
- 37. (fish adj3 capsul*).ti,ab.
- 38. icosapentaen*.ti,ab.
- 39. docosapentaen*.ti,ab.
- 40. (oil* adj3 (purslane or mustard* or candlenut* or stillingia or walnut*)).ti,ab.
- 41. 36 or 37 or 38 or 39 or 40
- 42. 33 and 41
- 43. 35 or 42

Embase Ovid

- 1. exp salmoniformes/ or tuna/
- 2. fish oil/
- 3. linseed oil/
- 4. linolenic acid/
- 5. Flax/
- 6. omega 3 fatty acid/
- 7. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.
- 8. (oil* adj3 (cod* or marin*)).ti,ab.
- 9. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.
- 10. (eicosapentaen* or icosapentaen*).ti,ab.
- 11. docosahexaen*.ti,ab.
- 12. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.
- 13. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.
- 14. (perilla* or linseed* or maxepa*).ti,ab.
- 15. (marin* adj3 lipid*).ti,ab.
- 16. (naudicelle* or herring* or sild).ti,ab.
- 17. (clupe* adj3 hareng*).ti,ab.
- 18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.
- 19. (salmo* adj3 trut*).ti,ab.
- 20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.
- 21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.
- 22. (crab or crabs or (cancer adj3 pagarus)).ti,ab.
- 23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
- 24. random\$.tw.
- 25. placebo\$.tw.
- 26. (doubl\$ adj blind\$).tw.
- 27. (singl\$ adj blind\$).tw.
- 28. double blind procedure/
- 29. randomized controlled trial/
- 30. single blind procedure/
- 31. 24 or 25 or 26 or 27 or 28 or 29 or 30
- 32. (animal/ or nonhuman/) not human/
- 33. 31 not 32
- 34. 23 and 33
- 35. (2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dd,em.

- 36. 34 and 35
- 37. exp salmonine/
- 38. (fish adj3 capsul*).ti,ab.
- 39. docosapentaen*.ti,ab.
- 40. (ALA or DHA or DPA or EPA).ti,ab.
- 41. (algal adj oil*).ti,ab.
- 42. 37 or 38 or 39 or 40 or 41
- 43. 33 and 42
- 44. 36 or 43

CONTRIBUTIONS OF AUTHORS

LH conceived this review and wrote the first draft of the protocol; LH drafted the searches, which were developed, refined, run and deduplicated by CB. ASA, NM, CB, XW, JSB, TJB, SH, OFJ, SMAA, FS, KHOD and LH screened titles and abstracts; ASA, JSB, SMAA, SH, NM, XW and LH assessed full-text papers for inclusion; LH, SH and JSB searched trials registers and assessed entries for inclusion; XW, NM, LH and ASA located full texts, LH and ASA managed assessment and collection of titles, abstracts and full texts, data extraction and 'Risk of bias' assessment; all authors carried out data extraction and assessed risk of bias. LH, KHOD and JSB designed 'Risk of bias' assessment; JSB, KHOD, SMAA, SH, TJB, ASA and LH wrote to trial authors; LH, KHOD, JSB, TJB and ASA carried out data checks; JSB, TJB, SMAA, XW, LH and ASA tabulated intake and status data. NM, CB, FS, KHOD, JSB and LH provided methodological support. ASA and LH entered data into Review Manager 5 and ran meta-analyses, carried out sensitivity analyses and subgrouping. LH carried out the meta-regression, wrote the first draft of the review, and wrote the World Health Organization report. LH and ASA carried out GRADE assessment and interpretation. All review authors critically read and commented on the final draft, and agreed it for submission. LH is the guarantor.

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 WHO NUGAG Subgroup on Diet and Health requested and funded this systematic review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to omit small trials (that randomised fewer than 100 participants) due to concerns over small study bias and the consequent potential for random error to result in false positive conclusions (Roberts 2015).

To ensure that the largest body of RCT evidence was considered in the formulation of recommendations, the WHO NUGAG Subgroup on Diet and Health requested that trials of all sizes be included as long as they fit the other inclusion criteria.

To do this we re-assessed all titles and abstracts in duplicate to ensure that we collected all smaller as well as larger trials, and carried out a sensitivity analysis omitting trials that had randomised fewer than 100 participants, as well as omitting trials that randomised fewer than 250 participants (this sensitivity analysis was already agreed).

We were also requested by WHO NUGAG Subgroup on Diet and Health to add the following sensitivity analyses:

- 1. only including trials with a low risk of bias from compliance, and
- 2. only including trials at low summary risk of bias.

We intended to assess causality (another aspect of performance bias, where a trial intervention included changes other than the change in PUFA intake, when there would be high risk of bias) but as we limited inclusion to trials where the dietary changes were limited to dietary fats this was not needed and so omitted. We also planned to assess whether a trial was pre-registered on a trials register (registration date is before outcome data collection begins; Roberts 2015) but we incorporated the issue of pre-registration into selective outcome reporting and did not use a separate form of assessment. We recorded funding data in the Characteristics of included studies and did not use them as a separate issue for assessing risk of bias, as recommended (Higgins 2011a).

INDEX TERMS

Medical Subject Headings (MeSH)

*Primary Prevention; *Secondary Prevention; Adiposity; Cardiovascular Diseases [mortality; *prevention & control]; Cause of Death; Cholesterol [blood]; Fatty Acids, Unsaturated [*administration & dosage; adverse effects]; Lipoproteins, HDL [blood]; Lipoproteins, LDL [blood]; Randomized Controlled Trials as Topic; Triglycerides [blood]; Weight Gain

MeSH check words

Adult; Humans